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HYDATID DISEASE OF THE FALLOPIAN TUBES

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Hydatid disease (echinococcosis) of the Fallopian tubes, whether primary or secondary, is a condition of great rarity. Craig and Faust[1] state that the incidence of hydatid disease in the female pelvis is 0·2% of all the sites where it may be found and that most of the cases are secondary to infection elsewhere. The present case was secondary to a widespread infection of the abdomen and pelvis of at least 7 years' duration.

CASE REPORT

A Bantu female, aged 41, was admitted to the Provincial Hospital, Port Elizabeth, on 18 November 1953, from a sheep-farming district. She was complaining of persistent discomfort in her abdomen which had been present for 7 years, and an abdominal swelling which had steadily been increasing in size for the past 4 years. She also complained of a burning pain in the right iliac fossa for 1 year and dysuria. The menstrual cycle was 5-10/30 and was accompanied by severe dysmenorrhœa.

Obstetric History. Three full-term pregnancies. The first, in 1938, was terminated by Caesarean section on account of an abdominal tumour; the patient did not know the nature of the tumour or whether it was removed; the baby lived for 7 days. This was followed in 1939 and 1942 by two normal confinements; both children are alive and well.

Past History. Laparotomy for hydatid disease in 1946.

Examination. The patient was well nourished and in a fairly good condition. The heart and lungs were normal, the blood pressure was 170/110 mm. Hg, and nothing abnormal was found in the urine.

A large irregular mass, arising out of the pelvis, filled the whole of the lower abdomen. It was partly solid and partly cystic and was very tender on palpation. Another very mobile mass was felt just above the umbilicus. The liver extended for 2 inches below the costal margin; it was hard and slightly tender.

Per vaginam. The vaginal walls were healthy. The cervix was lacerated but the body of the uterus could not be identified. In the anterior fornix several cystic and solid lumps were palpated and in the pouch of Douglas there was a large cystic swelling, part of which protruded into the vagina.

The *blood count* (21 November) showed: haemoglobin 108%; erythrocytes 5,530,000 per c. mm.; leucocytes 5,500 per c. mm. (neutrophils 39%, lymphocytes 56%, monophils 1%, eosinophils 4%). The erythrocyte sedimentation rate was 17 mm. for the first hour. The Wassermann reaction was negative. A diagnosis was made of a recurrence of the hydatid cysts.

Operation. On 25 November, the abdomen was opened through a left paramedian incision. Numerous hydatid cysts, both small and large, were found all over the abdomen. Those attached to the greater omentum, transverse mesocolon, pelvic mesocolon, the bowel and the parietes were excised. The uterus, tubes and ovaries were buried in a mass of cysts and adhesions. There was a large cystic swelling between the uterus and bladder and another between the uterus and rectum. The left Fallopian tube was grossly distended and was full of daughter cysts. The right tube was narrow for the first 2 inches and then opened into a large

Fig. 1. T=enlarged left Fallopian tube containing hydatid cysts. U=uterus. C=isolated hydatid cysts attached to the broad ligament.

cyst containing at least half a pint of daughter cysts. Other cysts were attached to the broad ligaments and side walls of the pelvis and some burrowed under the peritoneum.

A subtotal hysterectomy and bilateral salpingo-oophorectomy were performed and the pelvis cleared of all visible cysts. It was not possible to remove the cervix. As the patient was very shocked, no attempt was made to deal with the cysts in the liver and right kidney at this stage.

Once the patient had recovered from her operation, convalescence was normal except for slight wound sepsis, which soon settled.

Second Operation. A surgical colleague was asked to deal with the upper abdominal lesions, and on 5 January 1954 an operation was performed by Mr. F. Counihan. Through a right Kocher's incision the multiple cysts in the liver and right kidney were aspirated and 2% formalin solution injected. Convalescence was normal and the patient was discharged from hospital 13 days later.

The *specimen* (Fig. 1) shows a uterus, enlarged to twice the normal size, containing a submucous fibroid but no visible hydatid cysts. The right Fallopian tube, which is narrow for the proximal 2 inches, opens into a large cyst, full of daughter cysts, which had to be evacuated during the operation. The left tube is 7 inches long and 4 inches in circumference and the abdominal ostium is sealed off. The tube wall is very thin and transparent and the daughter cysts can clearly be seen. The ovaries were not identified and were probably buried among the numerous cysts and adhesions in the pelvis. The specimen has been preserved intact and no attempt made to open up the tube.

COMMENT

Cases of primary hydatid disease of the Fallopian tube have been described by Eden,[2] Jorge and Berisso,[3] and Holzbach,[4] among others. In Eden's case, which occurred in a woman who had lived all her life in London and had never kept an animal in the house, the right tube only was affected and the rest of the abdominal viscera were free from the disease. Eden considered the primary lodgment in most cases to be beneath the peritoneum in the pelvic cellular tissue of the pouch of Douglas. From there the ova burrow in all directions and come into relation with the uterus, bladder, rectum, ovaries and Fallopian tubes. In the present case it would appear that the infection spread along similar lines. Jorge and Berisso described a solitary subserous hydatid cyst of the proximal half of the right Fallopian tube; no other cysts were found in the abdomen. Holzbach's case occurred in a patient whom he was treating for sterility and whose tubes were found to be blocked on insufflation. A laparotomy was performed and hydatid disease of the right tube was discovered.

Toole,[5] and most authors, regard primary infection of the tube as arising either from the blood stream or else from a penetration by the embryo through the rectum or vagina. On the other hand, Dew[6] states: 'Cysts of the Fallopian tube are invariably secondary cysts, the tube being stretched and more or less incorporated in the adventitia. Rarely, as in the case recorded by Bennie and Allen, the cyst may rupture into the lumen of the tube with or without intra-uterine discharge of the cyst contents. Clinically there may be pain in the lower part of the abdomen, variable pressure effects in the case of large cysts or menstrual irregularities, all of which may be accentuated if multiple cysts are present. The cyst may make its way into the pouch of Douglas and is often indistinguishable from an ovarian cyst.'

In our case the patient, who came from a sheep-farming district, was known to have had hydatid disease of the abdomen for at least 7 years and possibly much longer. It was not surprising that at operation numerous cysts were found throughout the abdomen and pelvis and that most of the abdominal viscera were extensively involved. Although it has been shown that the Fallopian tubes are among the very last organs to be affected by the disease, there was ample time and opportunity in this case for the disease to spread to the tubes, and their appearance was consistent with a very advanced state of infection. It is worth noting that, in spite of being surrounded and buried by hydatid cysts, the uterus remained unaffected. Evidently its resistance to the disease must be rated very high, although recently Hagberg and Maizels[7] have recorded a case of a solitary hydatid cyst of the uterus with no signs of the disease elsewhere in the body.

It is a matter for speculation whether the abdominal tumour that was responsible for the Caesarean section in 1938 was a large hydatid cyst or merely an ovarian cyst or a myoma. Whatever it may have been, it was followed by two normal confinements in the next 4 years, and 8 years elapsed before the laparotomy for hydatid disease was performed. The ultimate prognosis for this patient is poor and a recurrence within the next few years is almost certain to take place.

SUMMARY

Advanced hydatid disease (echinococcosis) of both Fallopian tubes, part of an extensive and oldstanding abdominal infection, is described in a multiparous Bantu female.

I wish to thank Dr. J. McLean, Medical Superintendent, Provincial Hospital, Port Elizabeth, for permission to report this case.

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4. Holzbach (1928): Schweiz. med. Wschr., **58**, 902.
5. Toole, H. (1935): Arch. klin. Chir., **184**, 185.
6. Dew, H. R. (1928): *Hydatid Disease*, p. 268. Sydney.
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UNION DEPARTMENT OF HEALTH BULLETIN

Union Department of Health Bulletin: Report for the 7 days ended 18 August 1955.

Plague, Smallpox: Nil.

Typhus Fever, Cape Province: No further cases have been reported from the Queenstown district since the notification of 21 July 1955. This area is now regarded as free from infection.

Epidemic Diseases in other Countries:

Plague: Nil.

Cholera in Calcutta (India).

Smallpox in Moulmein, Rangoon (Burma); Phnom-Penh (Cambodia); Allahabad, Bombay, Calcutta, Cuddalore, Kanpur, Lucknow, Nagpur, Visakhapatnam (India); Dacca, Karachi, Lahore (Pakistan); Mogadiscio (Somalia); Tanga (Tanganyika).

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VAN DIE REDAKSIE

VERSPREIDE LUPUS ERYTHEMATOSUS

Lupus erythematosus word soms as 'n seldsame siekte beskou, en baie mense is onbewus van sy uiteenlopende manifestasies. Dit behoort maklik te wees om die klassieke vorm van akute, verspreide lupus erythematosus by 'n pasiënt te diagnoseer. In 'n tipiese geval word 'n jong vrou, onder 30 jaar oud, skielik siek. Sy het 'n hoë koors, voel moeg en afgemat, en het eriteem in skoenlappervorm oor neus en wange, en pyne in die spiere en gewrigte. Wrywing mag voorkom in die borsvlies en hartsak, en die lewer, milt en limfkliere mag vergroot wees. Daar mag bloedarmoede, 'n gebrek aan witselle en 'n verhoogde besinkingsnelheid wees en die urine mag rooiselle, silinders en eiwit bevat. Die L.E.-toets is positief.

In teenstelling met so 'n skielike aanvang, mag die pasiënt al vir 'n lang tyd siekerig gewees het, vermoedelik aan rumatiekkoors, rumatiese gewrigsontsteking, nierliggaamontsteking, of Rayneaud se verskynsel. By sommige pasiënte skyn al die sisteme by die siekte betrokke te wees; by ander slegs een of twee organe. Die kliniese wisselvorme het aanleiding gegee tot 'n verskeidenheid klassifikasies. Huidartse onderskei die kroniese skyfvormige of omskrewe soort; die algemeenvoorkomend, verspreide of sisteemsoort van akute, subakute en kroniese aard; en die verwante aandoenings bekend as die Senear en Usher-sindroom en die Libman en Sacks-sindroom. Sommige dokters dink dat sisteemlupus erythematosus nie aan die skyfsoort verwant is nie, en afdoende bewys dat 'n verwantskap wel bestaan is nog nie gelewer nie. Dit is selde moontlik om 'n oorgang van een soort tot die ander by 'n besondere pasiënt waar te neem, maar dit is al by 'n groep pasiënte bewys dat die velaandoening eerstens in skyfvorm, dan subakuut en eindelik in akute sisteemvorm voortwoeker.

Die uiteenlopende en seldsame manifestasies van lupus erythematosus kan nie hier bespreek word nie, maar 'n paar punte mag wel vermeld word. Veral in die ledemate word die groot sowel as die klein gewrigte aangetas, en dus word ander siektes dikwels gediagnoseer voordat die aandoening as lupus erythematosus uitgeken word. Die asemhalingstelsel openbaar aantasting op verskillende maniere, bv. as long- en lugpypontsteking, uitvloeisels en hartverswakking. Benewens bloedarmoede en witselgebrek, mag die bloedbeeld 'n gebrek aan bloedplaatjies en eosinofiele sowel as bloedselontbinding en die teenwoordigheid van meer

EDITORIAL

DISSEMINATED LUPUS ERYTHEMATOSUS

Lupus erythematosus has been considered a rare disease and many have not been aware of its protean manifestations. The patient with classical acute disseminated lupus erythematosus should not present any difficulty in diagnosis. In a typical case a young woman under 30 years of age becomes suddenly ill with high fever, fatigue, exhaustion, erythema across the nose and cheeks (butterfly distribution) and pains in the muscles and joints; there may be friction rubs in the pleura and pericardium, enlargement of the liver, spleen and lymph glands, anaemia, leucopenia and raised sedimentation rate; the urine may contain red cells, casts and albumin. The L.E. test is positive.

Instead of such a sudden onset the patient may have had a long period of low health and may have been regarded as suffering from one of many diseases, e.g. rheumatic fever, rheumatoid arthritis, glomerulonephritis, Raynaud's phenomenon. In some patients all systems appear to be involved, in others only one or two organs. The clinical variations have led to many classifications. Dermatologists distinguish the chronic discoid or localized type, the generalized, disseminated or systemic types (acute, subacute and chronic) and the related conditions designated Senear-Usher syndrome and Libman-Sacks syndrome. There are some who consider systemic lupus erythematosus unrelated to the discoidal condition, and satisfactory proof of a relationship between the two conditions remains to be established. It is rarely possible to follow the transition in a single patient, but in groups of patients a progression of skin lesions from discoidal through subacute to acute systemic phases has been demonstrated.

Consideration cannot be given here to the various unusual manifestations of lupus erythematosus. A few points may however be mentioned. Thus for example the involvement of small and large joints, especially in the limbs, often leads to other conditions being diagnosed before lupus erythematosus is recognized. The respiratory system may show involvement in different ways, such as bronchopneumonia, effusions- and cardiac failure. In addition to anaemia and leuco,

plasmaglobulien toon. Die gammaglobulienfraksie behels die L.E.-plasmafaktor wat verantwoordelik is vir die L.E.-verskynsel en wat as kokarde van leukosiete en L.E.-selle in preparate van periferale bloed en beenmurg voorkom.

Toediening van kortikotrofien (ACTH), en die steroïede soos kortisoon, hidrokortisoon en fluorohidrokortisoon het 'n dramatiese en snelle verbetering by gevalle van beide akute verspreide en sistemiese lupus erythematosus bewerkstellig. Versigtigheid en oordeelkundigheid is egter noodsaaklik om te verhoed dat die behandeling self komplikasies veroorsaak. Baie van die manifestasies van hierdie siekte word deur hierdie middels verbeter, maar op andere het hul geen uitwerking nie. Dit is nog nie onteenseglik vasgestel of hierdie middels wel die sterftesyfer verminder nie. Die siekte mag binne 'n paar weke na die staking van behandeling hervat, maar soms verloop daar enige maande voordat dit gebeur. Die gebruik van steroïedmiddels is wesenlik simptomaties behandelend maar nie helend nie. Dit is nogtans moontlik dat hul onbekende faktore in staat mag stel om 'n meer permanente genesing te bewerkstellig. Chirurgiese en geneeskundige behandeling wat voorheen weens die pasiënt se neiging tot oorgevoeligheid afgeraai is, mag nou moontlik gemaak word. Mepakrien en chlorochine tel onder die middels wat òf alleen òf saam met steroïede gebruik word. Veral as die niere aangetas is, word die stikstofmosterds ook gebruik instede van die steroïede wat gewoonlik ondoeltreffend is. Verskeie voorsorgsmaatreëls, o.a. die gebruik van testosteroon om 'n negatiewe stikstofbalans en osteoporose te verhoed, word veiligheidshalwe getref. Suikersiekte en maagsere word ook op soortgelyke wyse beheer.

Haserick[1] het in die pasbenoemde *Journal of Chronic Diseases* 'n oorsig gelewer van die ongewone en atipiese manifestasies van lupus erythematosus. Hy het die waarde van geneesmiddels wat by die behandeling van 'n groep van 126 pasiënte in die Cleveland-kliniek in die V.S.A. gebruik was, bespreek. In dieselfde uitgawe bespreek Merrell en Shulman[2] die prognose van sistemiese lupus erythematosus, en doen Moore en Lutz[3] verslag oor 'n serologiese studie van die siekte se natuurhistorie.

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2. Merrell, M. en Shulman, L. E. (1955): *Ibid.*, **1**, 12.
3. Moore, J. E. en Lutz, W. B. (1955): *Ibid.*, **1**, 297.

penia, examination of the blood may reveal thrombocytopenia, eosinopenia and haemolysis; the plasma globulins are increased. The L.E. plasma factor is found within the gamma-globulin fraction, and is responsible for the L.E. phenomenon (rosettes of leucocytes and L.E. cells in preparations of peripheral blood and bone-marrow).

Dramatic and rapid improvement has been produced in acute disseminated or systemic lupus erythematosus by the administration of corticotrophin (ACTH) and steroids such as cortisone, hydrocortisone, and fluorohydrocortisone, but great care and judgment are required to prevent complications resulting from the treatment itself. Many of the manifestations are relieved by these drugs, but others are unaffected, and it is not yet properly established that they reduce the mortality. Relapse may occur within a few weeks after therapy is discontinued, but occasionally several months elapse before this occurs. The use of the steroid drugs is essentially symptomatic medication and not curative; however, steroidal therapy may enable unknown factors to produce a more permanent remission and may render possible surgical and medical treatment which would have been contra-indicated in former years by the tendency of the patient to over-react. Other drugs that are being used alone or with steroids include mepacrine and chloroquine, and nitrogen mustards, the latter especially when there is renal involvement, for which the steroids are usually ineffective. Various general supportive measures are taken, including the use of testosterone to prevent negative nitrogen balance and osteoporosis, and measures for the management of diabetes and ulcer.

The unusual and atypical manifestations of systemic lupus erythematosus, and the value of medicinal measures in a group of 126 patients treated at the Cleveland Clinic, U.S.A., since 1948 have been reviewed by Haserick,[1] in the newly named *Journal of Chronic Diseases.* In the same issue the prognosis in systemic lupus erythematosus is considered by Merrell and Shulman,[2] and a study of the natural history of the disease by serological methods is reported by Moore and Lutz.[3]

1. Haserick, J. R. (1955): J. Chron. Dis., **1**, 317.
2. Merrell, M. and Shulman, L. E. (1955): *Ibid.*, **1**, 12.
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THE SOUTH AFRICAN POLIO VACCINE

The first experimental polio vaccine was produced in 1934, but only since 1949, when the 3 types of polio virus were recognized and their cultivation in tissue culture achieved, has research been possible into the production of a preventive vaccine on a large scale. 'Killed' formolized vaccines have been prepared in more than one country. The lead was taken by the Salk vaccine in America, where the famous Field Trial was carried out in 1954, amid a blaze of publicity unprecedented in medical research and by no means confined to the USA. The research was also pursued in South Africa in the Poliomyelitis Research Foundation Laboratory, which was built and equipped by the Polio Fund generously subscribed for the purpose by the public of this country a few years ago. As a result of the work carried out there by Dr. J. S. Gear and his small band of co-workers, a South African formolized polio vaccine is now available for the protective inoculation of sections of the public.

There is good reason to hope that a living avirulent or attentuated polio virus will eventually be forthcoming, and the experience with other viral diseases

suggests that a virus of this type may be the ultimate solution of the problem of the prevention of poliomyelitis. In the meantime the available formol vaccines, which appear to afford a means of conferring immunity against the disease, even if with limitations, have been brought into use in certain countries.

A vital issue is the question of the safety of the vaccine, brought into prominence by recent events in America, and this and other questions were referred to a special committee of South African experts appointed by the Minister of Health to advise him on the use of poliomyelitis vaccine with special reference to the Foundation Laboratory's vaccine.

This Committee met on several occasions, and reviewed the Francis Report and all the developments which followed upon the institution of the mass immunization campaign in the USA. In particular it studied carefully the official report from the Surgeon General on the investigation that had been carried out into the Cutter disaster and the important recommendations which resulted from these investigations. It also carefully studied the records of the South African vaccine. At its final meeting it unanimously advised the Minister that the Foundation Laboratory's vaccine had been proved safe beyond all reasonable doubt and was probably efficacious.

Promptly upon the receipt of this advice the Minister, because of wide public interest, fostered by newspaper accounts, made a radio announcement and a press statement which is published on page 847 of this issue of the *Journal*.

It was regrettable that the Department of Health was not able immediately to publish a full technical report for the guidance of the medical profession. The Secretary for Health, however, instructed Dr. R. Turner, Senior Government Pathologist, Cape Town, and Adviser in Pathology to the Union Health Department, to draw up a full technical review for publication. This review naturally took time to compile and it is now published in this issue (page 833). It reflects the personal views of Dr. Turner but they are views which in the main are supported by the expert committee and the Department of Health. It also gives a full account of the information on which the Committee based its opinion.

The report concludes that a 'killed' formolized poliomyelitis vaccine of undoubted safety can now be consistently manufactured and that the vaccine produced at the Poliomyelitis Research Foundation Laboratory is of value in preventing paralytic poliomyelitis. It is cheaper than the American vaccine, which is not indeed at present available in South Africa. Owing to the first few batches being discarded because the expert committee advised (following on the Cutter accidents) that all batches should be re-tested before issue, the vaccine is at present in short supply; but there will soon be an abundant supply. These batches were discarded not because anything had been proved wrong with them—on the contrary—but because, owing to the presence of merthiolate preservative, they could not be re-tested.

Formol-killed vaccine may be but a start in the search for a prophylactic against paralytic poliomyelitis; but it appears to be a good start, even if in the future it should be replaced by live attenuated vaccine.

This production of a safe and probably effective vaccine in South Africa by Dr. Gear indicates that the publicly subscribed money invested in the Polio Foundation Research Laboratory has been well spent and is now paying excellent dividends. Dr. Gear has accomplished what he set out to do as Director of this Laboratory, viz. to produce a vaccine against poliomyelitis. He is to be congratulated and deserves a praise and appreciation of the medical profession of South Africa.

ACTIVE IMMUNIZATION AGAINST POLIOMYELITIS

A REVIEW

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This review has been written and is published at the request of the Secretary for Health of the Union of South Africa. It is an attempt to describe fully and fairly modern views and developments in regard to active immunization against poliomyelitis. It is hoped that the information contained in it will prove of some value to medical practitioners in South Africa in judging the value of poliomyelitis vaccine and in deciding whether or not to advise parents to have their children inoculated.

Before discussing the question of the value of the vaccine it is thought desirable to refer briefly to the virus and to describe shortly modern views on the epidemiology of the disease.

THE VIRUS

The poliomyelitis virus is one of the smallest viruses known, its approximate diameter being 20-30 m*u*.

Serological studies have shown that there are 3 distinct immunological types of virus and that type I is the most prevalent during epidemics. Numerous variant strains, differing in virulence and antigenic potency, have been described amongst these types, and one of the most notable is the Mahoney strain of type I, which is characterized by exceptional virulence attri-

buted to its alleged ability to multiply more rapidly than the others in non-nervous tissues. Animal experiments have indicated that little or no cross-immunization occurs between the different types, so that inoculation with one type protects only against homologous and not heterologous strains.

EPIDEMIOLOGY

Though viruses similar to that of poliomyelitis have been recovered from animals and though rodents have been successfully infected with human strains, there is no evidence that the disease in man is ever acquired from non-human sources. Natural infection always appears to be, directly or indirectly, from human to human and it seems possible that domestic flies may, on occasion, play a secondary role in the spread of the disease by mechanically transferring infected human faeces to foodstuffs. Persons who become infected may excrete the active virus particles in their nasopharyngeal secretions and faeces—in the former usually only for a few days and in the latter for a longer period which may extend over several weeks. It is such infected persons who are temporarily excreting the virus, principally in their faeces, that constitute the reservoirs for the spread of the disease. So abundantly may such persons excrete the virus that comparatively little difficulty is experienced in isolating it from small samples of the mixed sewage of cities during times of epidemics. Transfer of infection appears normally to occur from intimate personal contact such as prevails in families and between close associates. Thus the disease characteristically tends to spread from one family group to another.

Persons who become infected for the first time either develop no recognizable symptoms at all or develop a mild febrile illness which may be associated with slight upper respiratory or gastro-intestinal tract symptoms. This illness is so trivial and indefinite that it is not practical to diagnose it clinically with any certainty in the absence of paralytic signs, though its nature may be correctly suspected in times of epidemics. The firm diagnosis of non-paralytic poliomyelitis may only be made by special laboratory virological investigations. Only in an unfortunate few, about 0·1%, is the infection complicated by invasion of the central nervous system and the development of paralysis. Thus paralytic poliomyelitis is an uncommon complication of a very common illness and the disease may spread widely and silently through a whole community with only an odd case of paralysis here and there to indicate its presence.

Opportunities for infection with the poliomyelitis vaccine are so favourable that virtually every person becomes infected at some time or other with one or more types of the virus. As a result of such experiences a few die or become permanently paralysed but all who survive become immune. Normally such infection, with consequent immunity, is acquired in early childhood, so that in the past the main incidence of the disease has been in the age-group 1-5 years; hence the older name of infantile paralysis. In the last few decades in many countries, notably the USA, but also in the European population of South Africa, there has been a shift in the age limit towards the next highest group, 6-10 years, and the disease has also become commoner in adolescents and young adults. This shift in age-incidence has been clearly attributed to general improvement in sanitary conditions, which tend to postpone the age of primary infections. It is most unfortunate that the older a person is when he acquires the primary infection, the greater is his liability to develop a paralytic attack, particularly the fatal bulbospinal form of the disease.

Variations in the virulence of different strains would also appear to be an important factor in causing variations in the incidence of paralysis in different epidemics.

Resistance to Infection

In the past it was suggested that the immunity of the adult to paralytic poliomyelitis depended largely upon a gradual physiological maturation of the tissues which made them more resistant to invasion by the virus. An observation which is against this theory is that under uniform climatic conditions favouring uniform tissue maturation the average age of persons acquiring paralytic poliomyelitis is often higher in rural than in urban areas. Also it has been shown that in isolated communities, e.g. of Eskimos, the sudden introduction of poliomyelitis virus has caused numerous adult cases of paralytic disease.

Experimental animal work has clearly shown that infection is followed by the production of antiviral bodies associated with resistance to subsequent attempts at further infection, whilst extensive serological surveys have shown that in children infection is followed by persistent specific antibody response and that the majority of adults possess antibodies to all three types of virus. It is also of interest to note that one group of isolated Alaskan Eskimos who were investigated showed antibodies to one type of virus, which could be correlated by circumstantial evidence with an epidemic which had occurred amongst them some 20 years previously. That the possession of antibodies in humans consequent upon infection, usually acquired in early childhood, is associated with good immunity is evidenced by the rarity of paralytic poliomyelitis in adults. True, second attacks of paralytic poliomyelitis can occur despite this natural immunization, and it has been suggested that, as the ratio of second to first attacks is virtually the same as the latter to the whole population, infection causes no lasting immunity. This argument is, however, fallacious and second attacks may be explained readily by infection with a virus of a different type to that involved in the primary infection.

Overwhelming evidence based on epidemiological studies, animal experiments and serological surveys has thus clearly proved that lasting and effective immunity to the disease by all three types of virus is often acquired in childhood by specific and often clinically silent infections.

VACCINES

As there appears to be no hope of entirely banishing the poliomyelitis virus from our environment, as the isolation in quarantine of known cases in an attempt to limit the spread of infection appears to be futile

because for every recognized case of poliomyelitis infection there are numerous unsuspected cases, and as there is no known antibiotic substance or chemotherapeutic agent capable of aborting the disease (gamma globulin has also proved most disappointing in this regard and at best is only available in very limited amounts), our only hope in conquering the disease appears to lie in artificially stimulating a herd immunity by mass vaccination of children at risk with an efficient vaccine. The fact that lasting natural immunity is caused by uncontrolled infection lends great support to this hope.

It was realized a number of years ago that vaccines offered a promise in the conquest of poliomyelitis. Work towards this ideal was, however, hampered by lack of knowledge how to culture the virus artificially. Nevertheless, in 1934 Brodie and in 1935 Kolmer both prepared poliomyelitis vaccines. These vaccines were similar to the rabies vaccines still in current use in that they were composed of emulsions of central nervous tissues of infected monkeys. They differed from each other in that Brodie used formalin and Kolmer sodium ricinoleate to inactivate the virus. Following upon successful animal trials several large groups of children were inoculated with these vaccines. Though apparently no accidents occurred with the Brodie type, several cases of paralysis followed upon the use of the Kolmer vaccine and both were soon abandoned. Quite apart from the possibility of their containing live virus, such crude vaccines contain large amounts of antigenic nervous tissues which, by provoking antibodies which may be organ-specific but not species-specific, may cause allergic damage to the central nervous systems of the subjects, similarly to the neuroparalytic accidents which still complicate rabies vaccination.

Following upon the recognition by Bodian *et al.*[1] in 1949 that there were 3 types of the virus, the Typing Committee of the National Foundation for Infantile Paralysis of the USA proved that all known strains belonged to one or other of these 3 types.[2] In the same year Enders *et al.*[3] showed that the virus could be artificially propagated in tissue cultures. These discoveries gave the green go-ahead signal for a new attempt to manufacture poliomyelitis vaccine. The main theoretical question that then arose was: Should the vaccine be an inactivated 'killed' type or a 'living' but attenuated and avirulent type?

Living Attenuated Vaccine

The consensus of present opinion appears to be that living attenuated vaccines offer the greatest hope as effective prophylactic agents. As Cox[4] has pointed out, living virus vaccines produce immunity by the same process as nature, i.e. by inducing sub-clinical infections. By causing such an infection the virus particles multiply harmlessly in the tissues and so produce a sustained and gradually increasing antigenic stimulation which may result in an effective immunity. In this regard it is to be noted that the most outstanding successes with virus vaccines have been with smallpox, yellow fever, rabies, rinderpest and blue-tongue disease; all of which vaccines are composed of living but avirulent virus particles. A vaccine must, however, possess two essential basic qualities—safety and efficacy. Though there appears to be little doubt of the probable efficacy of a poliomyelitis vaccine composed of living but attenuated virus, we must be absolutely certain of the innocuousness of the viral strains of which it is composed. Such strains must be so attenuated that there is no danger whatever of their invading the central nervous system and causing paralysis, and they must also possess such a low potential for virulence as to be incapable of regaining such properties in their human host. At the same time these strains must still retain their essential antigenic properties to a degree of being capable of stimulating significant amounts of specific antibody.

Consequently a poliomyelitis vaccine must be trivalent, so as to be effective against all three types of the virus. Although avirulent strains of all 3 types are now available, sufficient work has not as yet been done to determine their value and safety. Koprowski *et al.*[5] have adapted the TN strain of type-II virus to cotton rats and have proved by experiments in monkeys and in human volunteers that this strain is avirulent for both when administered by mouth, and is still antigenic. Cox[6] has also adapted the MEFI strain of type II to the chick embryo. This avianized strain has been proved to be non-paralytogenic and non-lethal when injected intracerebrally into monkeys and it gives an immunogenic response when given intramuscularly or orally to chimpanzees. There is every hope that in the near future it will be practical to manufacture a safe and efficaceous trivalent vaccine composed of living attenuated virus particles. How long it will be before such a vaccine is available cannot be predicted with any certainty at this stage, but it will probably not be for several years as much research still has to be done. Cox, however, is most optimistic and states that 'the tools and methods are at hand to do the job'.

It would appear that many American and British authorities have centred their hopes on the early discovery of a 'living' vaccine, and it is presumably with this object in view that the Medical Research Council of Great Britain is sending a unit to Fajara in Gambia, where there is reason to believe strains of low virulence may be found.

Killed Vaccines

With 'killed' vaccines the opposite qualities apparently hold true—theoretically there should be little doubt about their safety but there is some doubt about their efficacy. 'Killed' poliomyelitis vaccines may be valueless for two reasons. Firstly the chemical or physical agent used to 'kill' the virus particles may at the same time largely destroy their antigenicity. Secondly, though antigenic potency may be little affected by the lethal agent, the amount of 'dead' antigen in the finished vaccine may be too small to provoke a significant antibody response. Thus, though the titre of the tissue-culture suspension of virus may be high, e.g. 10^6, which is over 1,000,000 particles per ml., the virus is so very small that the actual bulk of the antigenic material may be infinitesimal. Thus, the mass of 1,000,000 poliomyelitis virus particles is only equivalent to the mass of a few staphylococci. Can such a tiny amount of

antigenic material provoke an adequate immunity response? This would appear to be doubtful, though it is possible that the antigenicity of such a vaccine depends upon the number of antigenic particles rather than their mass. This, however, is a problem still to be solved. True, it is possible to concentrate the virus suspension as obtained from tissue cultures, but if high concentrations are required, e.g. 1,000-fold, then the possibility of manufacturing effective vaccines from tissue cultures may become impracticable on a large scale as well as exorbitantly expensive. Nevertheless, though there has been doubt whether it is practical or even possible to manufacture an effective 'killed' vaccine, there is hope that this can be accomplished.

THE SALK VACCINE

Salk, who was financially supported in his work by the National Foundation for Infantile Paralysis of the USA, has claimed that he has produced an effective 'killed' vaccine. In this vaccine he used formaldehyde to inactivate the virus. His fundamental experiment was to show that, if a suspension of poliomyelitis virus particles grown in kidney tissue culture with a final titre of 10^6 is treated at 37°C in a medium of pH 7·0 with 1 in 4,000 formalin solution USP (i.e. a final concentration of 0·009% of formaldehyde) and if these conditions are kept constant, there is a steady loss in infectivity with virtually no loss of antigenicity.[7]

Based on these experimental findings, Salk plotted a graph illustrating the logarithmic fall in the infective titre of the virus suspensions on incubation with 1 in 4,000 formalin against time as expressed in hours (Fig. 1). He found that in the higher titres (it was not practical to test the lower) the fall in rate of the infectivity titre appeared to follow a straight line. This constant rate of fall under constant conditions indicated that the suspension was homogeneous and that the combination of formalin with the virus particles was 'in accordance with the laws that govern a first-order chemical reaction'. Presuming this interpretation to be correct, Salk, by extrapolating this line so that it crossed the time abscissa, was able to predict that, at the end of 72 hours of incubation, there should theoretically only be one living virus particle left per ml. and that, at the end of 9 days, there should be only one living particle per million million ml., which is approximately a million tons of culture fluid. He also showed that, after such prolonged incubation with weak formalin solution, there was no appreciable loss of antigenicity. The basic foundations for the manufacture of a formalin-killed vaccine were thus laid. Moreover, this method of formalin inactivation apparently contained a built-in safety factor in that it appeared virtually impossible for any virus particles to escape the lethal effect of the formalin.

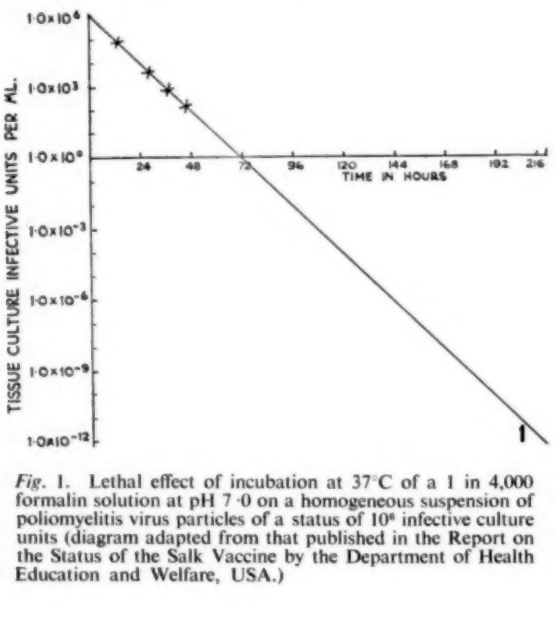

Fig. 1. Lethal effect of incubation at 37°C of a 1 in 4,000 formalin solution at pH 7·0 on a homogeneous suspension of poliomyelitis virus particles of a status of 10^6 infective culture units (diagram adapted from that published in the Report on the Status of the Salk Vaccine by the Department of Health Education and Welfare, USA.)

Salk next proceeded, in 1953, to manufacture experimental batches of vaccine. This was a trivalent vaccine employing the following strains of virus: Type I—Mahoney, type II—MEF and type III—Saukett. The primary consideration in the selection of these strains was doubtlessly their antigenic potency, whilst marked virulence, owing to the built-in safety factor, was not considered to be a disadvantage. Monovalent lots of the virus were grown on monkey kidney tissue cultures according to the method perfected by the Connaught Laboratories of Toronto, Canada, for the bulk growing of poliomyelitis virus. These lots were then inactivated with formalin and finally pooled to form a trivalent batch of vaccine. Antibiotics were added to the culture media to combat any possible bacterial contamination and, in some batches, an attempt was made to reinforce antigenicity by the addition of suitable adjuvants. 'Merthiolate' was finally added to each batch as a bacteriostatic. Suitable safety tests were carried out at different stages on all batches before they were issued for use.

In preliminary clinical trials Salk inoculated 5,320 volunteers with this vaccine over the period extending from May 1953 to March 1954. Apart from a few slight reactions, which were apparently due to sensitivity to the penicillin contained in the vaccine, there were no untoward effects, and serological tests showed that antibody production to all three viruses was stimulated. Thus these preliminary trials indicated that the vaccine was safe and suggested that it possessed some efficacy.

These promising results led to the conclusion of arrangements for extensive field-trials during the spring of 1954 to be sponsored by the National Foundation for Infantile Paralysis (NFIP).

Two commercial firms (Parke Davis and Eli Lilly) undertook to manufacture the vaccine required for these trials on behalf of the NFIP. This vaccine was to be manufactured according to the specifications for minimum requirements furnished by the NFIP and based upon the recommendations of its Vaccine Committee. Since safety was recognized as being of the utmost concern, a Committee also advised that the safety tests on all batches of vaccine should be carried out by 3 independent laboratories, so that 'chances of error will be remote indeed'. The 3 laboratories required to

undertake these tests were: (*a*) the laboratory of the manufacturer, (*b*) the Laboratory of Biologics Control (LBC) of the National Institutes of Health (NIH) of the Federal Public Health Service of the USA, and (*c*) Salk's own laboratory.

The stage was thus set to commence the field trials when, in March 1954, the laboratories responsible for the testing of the vaccine reported that tests for live virus in the vaccine had proved positive in 4 out of 6 batches. This finding naturally caused serious concern and the date for the commencement of the field trials was postponed. Various meetings of responsible bodies were held and, after carefully reviewing the situation, it was decided to establish stricter processing controls. Salk also carried out additional clinical trials so that later in April he was able to report that he had vaccinated a total of 7,507 children without untoward effects. On this additional evidence it was now considered that the vaccine had been proved safe, so that the field trials could be commenced.

THE FIELD TRIALS

The field trials of the Salk vaccine in the USA were commenced in May 1954, just before the summer poliomyelitis season. They were conducted over 211 study areas in 44 States. These study areas were specially selected and represented those localities in which the highest incidence of paralytic poliomyelitis in children between the ages of 6 and 9 years had occurred in the preceding 5 years. They were, therefore, areas in which the highest incidence of the disease was to be expected in children of the first 3 school grades during 1954.

The study areas were divided, on a voluntary basis, into 2 categories—the observed control areas and the placebo control areas. In the former areas 221,988 children in the 2nd grade of school (average age 7 years) were each inoculated with 3 doses of vaccine at fortnightly intervals, whilst the children in the 1st and 3rd grades acted as controls. In the latter areas 200,745 children in the first 3 school grades were inoculated with the vaccine, whilst 201,229 children from the same grades were inoculated with placebo which contained exactly the same ingredients as the vaccine except for virus particles. The children of the placebo group thus acted as perfect controls for the vaccinated children and any bias was avoided by so arranging the inoculations that it was not known until the final analysis who had received courses of vaccine and who placebo.

All the inoculations were completed in June 1954, and the children in both study areas were kept under medical observation for a period of about 6 months. Next, the results of the observations were carefully collected, collated and analysed by Dr. T. Francis, who had been appointed as chief of the Vaccine Evaluation Centre which had been established by the University of Michigan in joint sponsorship with the NFIP. Finally, a report on the evaluation of the trial was presented by Francis at Ann Arbor on 12 May 1955.[8] The analysis was chiefly in regard to the safety and efficacy of the vaccine.

There were two possible sources of danger from the vaccine, viz. (*a*) the presence of live virus particles, and (*b*) the presence of other harmful ingredients.

Though the incidence of paralytic poliomyelitis in the study areas proved to be 18% below the average in these areas for the previous 5 years, its incidence per 100,000 of population was nevertheless 26% higher than in the non-study areas. This evidence of a higher rate in the study areas was interpreted as indicating the correctness of the prediction that these areas would suffer a high incidence of the disease in 1954.

Though there were 129 cases of presumed poliomyelitis reported in the study areas during the month following the vaccinations, according to the report there was 'no evidence of disproportionate frequency of paralytic poliomyelitis in vaccinated or inoculated children up to 4 weeks after the conclusion of the vaccinations nor was there any indication of selective localization of paralysis when present'. There is therefore no evidence that the vaccine used in the field trials—

(*a*) caused any cases of paralytic poliomyelitis due to the presence of live virus in any of the batches of vaccine used, or

(*b*) provoked any paralysis in children who were incubating the disease at the time of their inoculations.

As regards possible harmful effects from other ingredients in the vaccine, all possibilities appear to have been explored carefully with negative results. Thus, a study of the school absentee rate indicated that there was 'a lack of significant untoward reactions to the vaccine', whilst a study of the nature of all reactions which were specifically reported showed the following results:

	Minor Reactions	*Major Reactions*
Placebo Control Areas		
Vaccinated	0·4%	0·004%
Placebo Controls	0·4%	0·006%
Observed Control Areas		
Vaccinated	0·7%	0·003%

These results indicated that 'reactions' were very few and no more common in the vaccinated children than in the controls. ('Minor reactions' included fainting, nausea, dizziness, slight rash and cold, whilst 'major reactions' covered such conditions as severe rashes, high fevers, severe pains in arms and legs, any paralysis or major disease of the nervous system, and any diseases of the kidneys.)

It was thought remotely possible that traces of monkey renal protein from the culture media in which the virus was grown might cause localized allergic damage to the kidneys of the inoculated children but there was no suggestion that this had occurred. Thus, though there were 7 cases of some form of nephritis or renal infection reported amongst the 29 vaccinated or control children who developed major reactions, there was no evidence in these cases of 'special selectivity in regard to the vaccine'. Moreover, exhaustive renal function tests and Addis counts carried out in small groups of vaccinated and control children showed no signs of renal impairment, and the assay of 100 paired sera, collected before and after the full courses of vaccination, showed no suggestion of the development of complement-fixation antibodies to monkey kidney tissue except in the case of one child who had received a vaccine containing an adjuvant, and this case was considered to be of doubtful significance.

Though it is very open to question whether the Rh antigens occur in tissues other than erythrocytes, it was also feared that any Rh factor possibly present in the traces of kidney tissue in the vaccine might cause Rh sensitization in Rh-negative children. Though the data for analysis were admittedly meagre, there was no evidence that this had occurred in any child investigated.

Finally, it was feared that the vaccination procedure, particularly when one syringe was used to inoculate more than one child, might have led to the transmission of infectious or serum jaundice. An analysis of the observations, however, failed to reveal any 'significant difference in the hepatitis experience of inoculated and non-inoculated children'. The total evidence of the field trials in regard to safety thus was that the vaccine used had proved quite harmless.

The evidence for *the efficacy of the vaccine* may be considered under two headings—serological and epidemiological:

The *serological* evidence consisted of measuring the antibody response of the vaccine by assaying samples of serum from the vaccinated children. Titrations of sera, collected before the first inoculations and 2 weeks after the courses were completed, as well as in the uninoculated children of the observed study areas, were not complete at the time of publication of the reports. The results of titrations of sera from 9,000 children were, however, tabulated. The tables showed that much of the vaccine was antigenic and had stimulated the production of protective antibodies in the vaccinated children. The assays also indicated that the potency of different batches of vaccine varied so that they could be classified into good, moderate and poor categories. Thus, there were a few batches that were found to be definitely poor in potency, either causing no antibody response or only a trace reaction, particularly in respect to the important type-I component. The lack of potency in these vaccines has since been shown to have been due to the merthiolate used in the vaccine as a preservative. Data from the third bleedings, which took

place some 5 months after the vaccinations, were 'incomplete and irregular', but the report stated: 'Nevertheless the accumulated results indicate that when good antibody response resulted from vaccination, the effect was maintained with but moderate decline after 5 months'.

The serological studies were, therefore, somewhat disappointing in indicating that some of the batches of vaccine used had been impotent, but they were otherwise most promising in indicating that formolized 'dead' poliomyelitis vaccine was capable of stimulating a significant and sustained protective antibody response.

The *epidemiological* evidence as to the value of the vaccine was assessed by comparing the poliomyelitis attack rates in the vaccinated and control children over a period of approximately 6 months. During this period 1,013 cases of presumed poliomyelitis, both non-paralytic and paralytic, were observed in the population of the study areas, and analysis of the figures indicates that in the placebo control areas the vaccine was 72% effective in preventing poliomyelitis and in the observed control areas it was 62% effective.

Steps were then taken to refine this analysis. The first step in the refinement was to eliminate the non-paralytic cases and to estimate the effect of the vaccine in preventing bulbospinal and spinal paralytic forms of the disease. This investigation, in the placebo control areas, gave the most striking result in regard to the prevention of the bulbospinal paralysis as the vaccine proved to be 94% effective (with a lower limit of 81%) in preventing this dreaded form of the disease. In the observed areas a much poorer result was obtained, the vaccine being only about 50% effective (with a lower limit of 19%) in preventing bulbospinal paralysis. The effectiveness in preventing spinal paralysis in the placebo control areas was only 60%, with a lower limit of 39%, and in the observed control areas it was about the same.

The next step in the refined analysis, and one which was designed to give greater confidence in the acceptance of results, was to compare only those cases in which the clinical diagnosis of paralytic poliomyelitis had been confirmed by suitable laboratory virological investigations. In this analysis the effectiveness of the vaccine against spinal paralysis was virtually the same in both placebo and observed control areas, being 82% in the former, with a lower limit of 65%, and 81% in the latter, with a lower limit of 64%, whilst in the placebo areas the effectiveness against the bulbospinal type of the disease was 91%, and in the observed control areas 60%.

The final analysis was to examine the efficacy of the vaccine in regard to the different types of virus infection. In the placebo control areas, the vaccine was found to be 68% effective against type I, 100% (with 0·5 significance) against type II and 92% against type III. In the observed control areas the same trend was noted but the calculated effectiveness was less.

In its conclusions the report states that 'from these data it is not possible to select a single value giving numerical expression in a complete sense to the effectiveness of vaccine as a total experience'. Though the figures from the observed study areas are poorer than from the placebo control areas, there is greater confidence in the figures from the latter, which indicate 'that vaccination was 80-90% effective against paralytic poliomyelitis, that it was 60-70% effective against disease caused by type-I virus and 90% or more effective against that of type-II and type-III virus'.

The report is thus disappointing in that it was hoped, in keeping with other virus vaccines, that the efficacy of poliomyelitis vaccine would have proved nearer 100% in preventing paralytic disease. Much of the failure of the vaccine to accomplish this may, however, be attributed to the poor potency of some of the batches of vaccine used, particularly in regard to preventing type-I virus infections, and no doubt, when more consistently potent formolized vaccines are used, better protective results will be obtained. Thus, the efficacy of the vaccination appears to be most promising for the future. The report, however, gives no indication of how long the immunity lasts beyond 6 months. Whether the protective value of the vaccine will be transitory and lasting but over a period of a few years or whether it will be permanent, is a problem which can only be solved with time.

SALK'S FURTHER CONTRIBUTIONS

When Francis presented his report at Ann Arbor, Salk also read a paper,[9] in which he made a number of very important observations which may be summarized as follows:

Chemical treatment for the inactivation of the virus particles in the vaccine does not reduce to a measurable extent the antigenicity of the vaccine unless over-treatment is extended for a period which is 5 times longer than that required to destroy infectivity.

The quantity of virus which is required in poliomyelitis vaccine to produce a significant antibody response, is far less than the amount which would be anticipated from comparison with other microbial antigens. (Though the number of virus particles which is present in a dose of poliomyelitis vaccine is relatively large, the mass, as previously stated, is extremely small. One inference which may be drawn from the fact that a small dose of killed poliomyelitis vaccine produces a measurable antibody response is that the antigenicity of the vaccine depends not upon the mass but upon the number of virus particles present per dose. Presumably each virus particle is responsible for the production of a series of antibody molecules by the infected receptor cells.)

It is also to be noted that man is far more immunologically sensitive to poliomyelitis virus than are experimental animals, including monkeys. Potency tests in animals must, therefore, be carefully correlated with antigenic performance in man.

Some of the batches of vaccine which were used in the field trials were later found to possess little or no potency, particularly in regard to their type-I component. This loss of potency was found to be due to the destructive effect of merthiolate, which was used as a bacteriostatic preservative in the vaccine, on its antigenicity. This deleterious effect, which occured most rapidly at warm temperatures, also took place on refrigerator storage. It has since been shown that it is practical to neutralize the destructive effect of merthiolate on antigens by 'versine', a preparation produced by Eli Lilly. Other suitable chemicals which do not affect antigenicity may also be used as preservatives.

Formolized vaccines, with proper preservative agents, are stable substances which, on suitable storage, long maintain their potency.

Vaccines prepared in 1955 have shown a more consistent degree of satisfactory potency than those used in 1954 and, therefore, better results from vaccination are to be expected in the future.

Vaccine which is administered subcutaneously has been proved to give almost as good a quantitative antibody response as that given intramuscularly, but vaccine given intradermally gives a much poorer response. There is, therefore, no disadvantage in using the subcutaneous route if it is feared that the intramuscular route may exert a 'provoking' effect.

In children who have not been previously vaccinated or who have not suffered a natural infection, the first dose of vaccine causes a relatively sharp rise in antibody titre, which may become measurable between the 6th and 9th days. A further rise is caused by a second dose given 2 weeks later but there is little change following a

third dose after a similar interval. Thus in primary vaccination there appears to be no good purpose served in giving more than 2 inoculations at a fortnightly interval.

Following upon successful primary vaccination, there is a gradual fall in the antibody titre but, if a booster injection is given 7 or more months later, an exaggerated response is obtained (see Fig. 2). This exaggerated response appears to be due to a state of specific hyper-

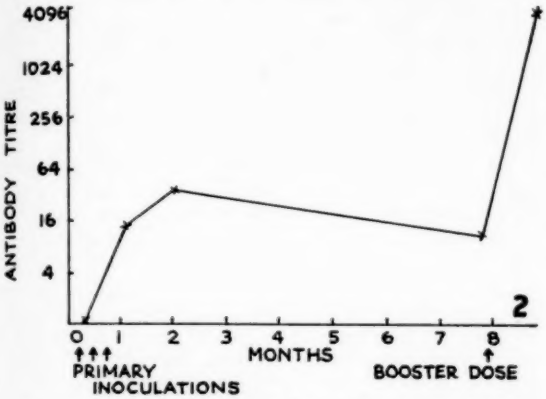

Fig. 2. Graph (adapted from Salk) showing the rise in titre of antibodies against type-I virus after 3 doses at 2-weeks intervals of a poliomyelitis formolized vaccine followed by the hyperactive response of a booster dose given approximately 7 months later.

activity which gradually develops after a particular immunological experience. How long this state persists is at present unknown, but it has been demonstrated over 2½ years after primary vaccination.

The level of the antibody titre which follows upon primary vaccination is generally lower than that which follows upon paralytic disease, but the level attained by a booster dose, after a suitably long interval, is higher than that provoked by disease. The booster effect in the hyperactive subject elicits not only a higher rise in the antibody titre but also a more rapid rise, which may be observed between the 4th and 8th day, by which latter time the maximum level is often already reached.

Natural infections, like primary vaccinations, are also followed by the gradual development of the hyperactive state; whilst natural infection occurring in a child who has had a primary vaccination some months previously also produces a booster effect.

Because of the booster effect, Salk advocates that a third injection should be given 7 or more months later than the primary vaccination of 2 doses.

It follows from Salk's paper that not only may stable, 'killed' poliomyelitis vaccines of consistent and satisfactory potency now be prepared, but that such vaccines may be of great value in the amelioration or prevention of paralytic poliomyelitis. The inferences which may be drawn from his findings in regard to children who have not been immunized by natural infections are as follows:

(*a*) If the child has not had a primary vaccination, it will possess no antibodies in its bloodstream to protect the nervous system from viral invasion.

(*b*) If the child has recently had a primary vaccination, it may or may not possess sufficient antibodies in its bloodstream to prevent invasion of the central nervous system, though its chances of doing so must be much greater than in the unvaccinated child.

(*c*) If the child has had a primary vaccination long enough previously to have brought him into an immunologically hyperactive state, on infection occurring a rise of antibodies may take place in his bloodstream rapid and high enough to effectively prevent invasion of the central nervous system.

(*d*) If a child has received a primary vaccination followed by a booster dose at an appropriate interval, it may well possess enough circulating antibodies to abort the infection before there is any chance of invasion of the central nervous system.

(*e*) If as a result of vaccination there are not enough antibodies in the bloodstream to totally prevent invasion of the central nervous system, such antibodies as are present may, nevertheless, prove of great value in counteracting the severity of paralytic complications.

EVENTS CONNECTED WITH MASS VACCINATIONS IN THE USA[10]

During February 1954, 5 commercial firms in the USA agreed to produce experimental batches of the vaccine on behalf of the NFIP, and the LBC undertook to cooperate in the testing of the vaccine. The 5 firms concerned were: Parke Davis Co., Eli Lilly Co., Wyeth Laboratories Inc., Pitman-Moore Co. and Cutter Laboratories.

In May 1954 the LBC issued a document, entitled 'Minimum Requirements, Poliomyelitis Vaccine', which was intended to be a provisional guide to manufacturers in regard to the standards required for the processing and testing of the vaccine.

In August 1954, in anticipation of success in the field trials, the firms made preparations for the large-scale commercial production of the vaccine, and they entered into agreements with the NFIP to supply it with 27 million c.c. of vaccine.

During the following month the LBC inspected the plants of these manufacturers and discussed with them various technical aspects of processing and testing, so as to be prepared to issue manufacturing licences as soon as the field trials were completed.

In November 1954 a sixth firm, Sharp and Dohme, joined the manufacturers.

In January 1955 the manufacturers began to submit protocols and samples from manufactured batches to the LBC.

On 12 April 1955 the Francis Report was published. Because of its favourable character, the LBC immediately officially issued 'Revised Provisional Minimum Requirements for Poliomyelitis Vaccine', i.e. official standards for purity, potency and safety, whilst on the same day the Secretary for Health, Education and Welfare issued manufacturing licences to the firms concerned. This was done on the recommendation of the Chief of the LBC,

transmitted through and approved by the Surgeon-General of the Public Health Service of the USA.

On the following 2 days the first batches of vaccine were issued for the mass vaccination campaign of children in the USA. The numbers of batches released were Cutter 6, Lilly 2, Parke Davis 3 and Pitman-Moore 2. These batches were released largely on inspection of the protocols (records kept by each manufacturer of the processing and testing of each individual batch of vaccine) and samples of only about half of these batches were subjected to full independent safety tests by the LBC.

By 27 April some 40 batches, totalling 10·5 million c.c. of vaccine, had been released.

On 27 April the LBC received information that 5 cases of paralytic poliomyelitis had occured amongst children in California who had received inoculations of vaccine some 10 or 11 days previously, and a case had also been reported the previous day from Chicago. These 6 children had received Cutter vaccine and there appeared to be presumptive evidence that the vaccine was the cause of the disease. On receipt of this information, the Surgeon-General immediately requested the Cutter laboratories to withdraw all vaccine and the firm promptly complied. As the cases of poliomyelitis had only occurred amongst children vaccinated with materials from one firm, it was decided to allow the campaign to continue with vaccine supplied by the other firms. Official investigations into the plant of the Cutter Laboratories and into the cases were immediately instituted. Also a special Poliomyelitis Surveillance Unit was set up at Atlanta for the rapid investigation of all cases reported as poliomyelitis, whilst the LBC began a series of tests on the Cutter vaccine. Next an *ad hoc* committee of 11 eminent virologists and immunologists was convened to advise the NIH, to review the situation, and to make recommendations. This committee endorsed the action taken by the Surgeon-General and, on its advice, the Chief of the LBC decided not to release any more batches of vaccine until a review of the Minimum Requirements had been completed. Finally, on 7 May, the Surgeon-General recommended that all vaccinations against poliomyelitis should be suspended until investigations had been completed.

Up to this time a total of 113 poliomyelitis cases with 5 deaths had been recognized amongst the 5½ million children vaccinated during the campaign. Sixty-nine of these cases (59 of which were paralytic) occurred amongst the 409,000 recipients of Cutter vaccine, giving an attack rate of 17 cases per 100,000 persons per month. Most of these cases were from California and Idaho.

Amongst the 4,985,000 children who had received vaccine manufactured by other firms, only 44 cases of poliomyelitis (19 of which were paralytic) were reported, giving an attack rate of less than one case per 100,000 of population per month.

Most of the reported poliomyelitic cases, when investigated, were found to be due to type-I virus.

An analysis of the figures indicated that, in the case of Cutter vaccine, the difference in the number of cases that had occurred and the number expected (35 and 5) was significant and so suggested an association between the occurrence of poliomyelitis and vaccination. In the case of the Wyeth vaccine the difference (11 and 2) was thought to be possibly significant, but the figures were considered to be too small to allow of a definite decision, whilst in the case of the Lilly, Parke Davis and Pitman-Moore vaccines, the numbers of cases of poliomyelitis reported were well within the range of expected chance. Sharp and Dohme had apparently supplied no vaccine up to this stage.

This evidence, therefore, strongly indicated that the Cutter vaccine was responsible for the accidents but only doubtfully suggested incrimination of the Wyeth vaccine and did not suggest that vaccine from the other manufacturers had caused any cases.

The evidence that Cutter vaccine had produced accidents due to the presence of live virus was also reinforced by the following facts:

(*a*) The interval between inoculations and the onset of paralysis (5-20 days) was significant and fitted in with geographical distribution and calendar time.

(*b*) The correlation between the site of injection and the extremity paralysed was good.

(*c*) The number of cases occurring amongst household associates (35 in the case of the Cutter vaccine, of which 29 were paralytic and 6 non-paralytic) indicated a causal relationship, and the interval between vaccination and the onset of the disease in parents and siblings approximated to 2 incubation periods.

Finally, it was concluded that the lack of cases in areas experiencing poliomyelitis at the time suggested that the cases were not due to provocation by the injections being given to subjects already incubating the disease.

THE CAUSES WHICH LED TO THE ACCIDENTS

The occurrence of the accidents due to the passing of live virus in the vaccine led to a thorough inquiry into the causes by the *ad hoc* committee. Salk's original experiments had indicated that the virus suspensions which he used were homogeneous and that the reaction between the formalin and the virus particles was of the first chemical order. There is, however, doubt as to whether such suspensions are always homogeneous and there is reason to believe that they may show a varying degree of heterogenicity due to the presence of virus particle aggregates of varying size and number. In the case of a heterogeneous suspension, a graph showing the fall in titre of active virus particles in the suspension as produced by the formalin and as plotted against time will not follow a straight line but a curve of varying shape (see Fig. 3). Thus, if the suspension is not homogeneous, the process, as described by Salk, possesses no defined built-in safety factor and it may be quite impossible to be certain at the end of the 9-day process whether the lot contains significant numbers of live virus particles or not. The question of the degree of heterogenicity of the virus suspensions probably largely depends upon the method of filtration of the monovalent lots and it has been suggested that with ultra-filtration procedures the filtrate is relatively homogeneous. Variations in the heterogenicity of monovalent suspensions, probably dependent on methods of preparation, may thus readily explain the passage of live virus particles in the vaccine and account

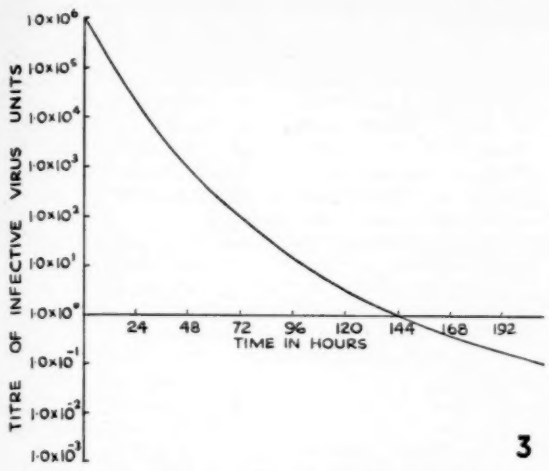

Fig. 3. Graph representing the fall in titre of infective virus units of a heterogeneous suspension of poliomyelitis virus when treated at 37° C and pH 7·0 with 1 in 4,000 formalin as plotted against time expressed in hours. The fall is not a straight line but a curve. Note: this is an imaginary curve not drawn from actual titrations.

for the varying experience of manufacturers in this regard.

The fact that the process of formalin inactivation often failed to 'kill' all virus particles was well exemplified by the experience of the manufacturers, who frequently detected live virus by tissue culture in the monovalent lots, even after re-processing them, sometimes several times. The manufacturers also, on occasion, detected live virus in the trivalent pools, although the monovalent lots of which they were composed had previously proved negative, so suggesting that the safety tests were inadequate. It is unfortunate that the firms did not always declare these difficulties to the NIH, in that they submitted only protocols of successful batches and made no reference to their unsuccessful efforts. The NIH thus appears to have been largely unaware of these serious difficulties experienced by the manufacturers.

Analysis of the safety testing also clearly showed that the tests required under the 'Provisional Minimum Requirements' were often quite inadequate to detect the passing of live virus. It was clear that monkeys were not sufficiently susceptible to infection with live virus for the animal inoculation tests to be reliable. The Provisional Minimum Requirements also required only 0·1% of the volume of each monovalent lot and of the trivalent pools to be subjected to tissue-culture tests. Statistical analysis has clearly shown that, when the lots or pools are small, 0·1% of their volume is too small to detect with reasonable certainty significant quantities of live virus. Thus, when only 40 to 45 c.c. of the monovalent lots and 140 c.c. of the trivalent pools are cultured, as was the case with one manufacturer, the mathematical chances of detecting 5 infective units per litre on tissue culture were only 60 to 70%.

Finally, it was unfortunate that Salk had selected the particularly virulent Mahoney strain for his type-I virus, which meant that, if particles of this virus escaped the lethal effects of the formalin, the chances of producing a serious infection with the vaccine were enhanced.

The analysis of the methods of processing and of safety-testing previously in use thus readily explained the causation of the accidents.

REVISION OF THE SAFETY TESTS

Following upon the investigations of the *ad hoc* committee of experts into the reliability and adequacy of the safety tests, it was decided to make certain modifications in this regard to the 'Minimum Requirements'. The principal amendments were as follows:

(*a*) All monovalent lots inactivated with 1 in 4,000 formalin solution were now required to pass 2 consecutive tissue-cultural tests separated by an interval of 3 days prior to the termination of the process, the minimum volume of the samples required for each of these tests to be not less than 500 c.c.

Re-activation, following upon the demonstration of live virus in the initial inactivation process, was to be limited to one additional process, which also is controlled by 2 separate negative cultural tests employing 500-c.c. samples.

(*b*) A negative culture test on not less than a 1,500-c.c. sample was required to be obtained from the trivalent pool.

(*c*) Finally, random samples from the filled containers were required to give negative virus cultural tests.

That the cultural tests for poliomyelitis virus are extremely sensitive is indicated by the experiments of Dulbecco and Vogt [11] on plaque formation. These experiments indicated that the formation of a plaque in a tissue culture may originate from a single virus unit, which is defined as the smallest virus unit that is inseparable by dilution. Wilson's criticism [12] that monkeys are not as sensitive to inoculations as are children has little bearing on the safety tests, which rely chiefly on the marked sensitivity of tissue cultures.

By following out the procedures required by the new modifications to Minimum Requirements, it has been calculated statistically that the chance of a batch of vaccine containing 5 or more live virus particles per litre (1,000 doses of vaccine) is less than 1 in 100,000 (i.e., that it would occur less than once in 100,000 times).

It was also recommended by the committee that less virulent type-I strains should be substituted for the Mahoney strain.

These amendments to Minimum Requirements were decided upon on 25 May 1955, and 2 days later the manufacturers' representatives agreed to support them. Meanwhile a team of public-health scientists and advisers visited the various factories in succession in order to re-clear batches of vaccine for re-starting the vaccination campaign at the end of May. Since then, according to newspaper reports, nearly 7,000,000 children in the USA have been vaccinated without any further accidents due to the passing of live virus.

That a safe 'killed' vaccine can be consistently prepared is, despite the Cutter accidents, thus evidenced by the field trials, by the later experience of American manufacturers and by experience in Canada, where over 800,000

children, and in Denmark, where over 400,000 children have been vaccinated to date with Salk-type vaccine and without untoward effects.

There is also sound reason to believe that the new safety tests are sufficiently reliable and adequate to guarantee beyond all reasonable doubt the safety of any batch of vaccine in regard to the presence of live virus particles.

THE SOUTH AFRICAN VACCINE

Following upon the severe epidemics of poliomyelitis which occured in South Africa after the last war, a large sum of money was raised by generous public subscription in the Union for the purpose of encouraging research into the disease and with the main object of obtaining a cure. This money has been wisely used to build, equip and, with the aid of government grants, to maintain the Poliomyelitis Research Foundation Laboratories at Rietfontein. Dr. J. H. S. Gear, who had had much previous experience in the manufacture of typhus, yellow fever and influenza vaccines, was appointed as its medical director. Though research investigations into many other important virus diseases affecting man in Southern Africa have been and are being undertaken by this laboratory, its main field of interest has naturally been in connection with poliomyelitis.

As soon as the basic knowledge that there were only three immunological types of the poliomyelitis virus and that these types could be artificially propagated on tissue cultures was established by overseas discoveries, Dr. Gear and his team under Dr. P. D. Winter set out to make a vaccine. Though their efforts were independent, they kept in close liaison with overseas authorities, particularly in the USA, and they gratefully acknowledge the advice and assistance received from Dr. T. H. Weller, Dr. J. E. Salk and Dr. Sven Gard, who were engaged on the same research problem. The only special advantage that they appeared to have was that there was a readier supply of monkeys in South Africa for experimental work than in other countries.

The vaccine that they decided upon was a 'killed' formolized vaccine very similar to that prepared by Salk. The method of manufacture adopted was to prepare monovalent-type suspensions of poliomyelitis virus particles from monkey kidney cultures. The titre of the suspensions obtained was generally slightly over 10^6. These lots were first clarified by coarse filtration and then subjected to ultra-filtration through special sinter-glass filters so as to exclude any possible contaminating bacteria and to produce a relatively homogeneous suspension. This filtration causes some slight fall in titre. The lots were then inactivated by incubation with formalin solution at pH 7·0 and at 37° C for 10 days. In the earlier batches, following upon American advice, 1 in 4,000 formalin solution was used but in the later batches this has been replaced by 1 in 2,000. These monovalent lots were then stored with the formalin unneutralized at ice-box temperature for 2-3 months. The free formalin was then neutralized by sodium bisulphite, and tissue-culture tests were carried out to ensure that the lots were free of live virus particles. Monovalent lots of the three different types were then mixed to form a trivalent pool. Tissue-culture tests were again set up, as well as monkey inoculation tests employing both the intracerebral and intramuscular routes for injection. Other suitable tests were next carried out to ensure that the products were sterile and, in particular, free of tubercle bacilli, lymphocytic choriomeningitic virus, etc. Potency tests were then carried out and, if the batch proved satisfactory in all respects, it was ampouled for issue. Before issue, however, a number of ampoules are also tested for live virus as a final precaution to ensure that no contamination has occured during the manufacturing process.

As penicillin and streptomycin are employed in the tissue cultures to combat any possible bacterial contamination, traces of these antibiotic substances may occur in the vaccine. No adjuvants are added and no merthiolate is used as a bacteriostatic.

The South African vaccine differs from the Salk in several respects. The strains of virus of which it is composed are the Brunhilda (type-I), the Collans (type-II) and the Templeon (type-III). The Brunhilda is the same strain as that used in the Danish vaccine, in which the Mahoney has been specifically prohibited. The Collans and the Templeon strains are local strains obtained in the Union. The strains employed in the South African vaccine are virulent strains but are not as virulent as the notorious Mahoney strain to which has been attributed the majority of the American accidents.

The inactivating process which is now carried out employs 1 in 2,000 formalin. Following upon the report of the Cutter accidents, the Advisory Committee of Experts to the Minister of Health advised that the strength of the formalin solution used for inactivation should be doubled. This extra precaution was taken because it was thought that it would increase the safety measures, and experimental evidence had indicated that it would not significantly alter the antigenicity of the vaccine.

The lots of vaccine are also stored with formalin at ice-box temperatures for 2-3 months before the formalin is neutralized. This procedure also apparently does not affect antigenicity and is calculated to add to safety. A more recent improvement, which was suggested by Prof. M. van den Ende and Dr. A. Polson, of Cape Town, has been to treat the vaccine with chloroform so as to remove the greater part of the foreign monkey kidney proteins.

The tissue-culture tests carried out on the earlier batches of vaccine were more extensive than those required by the original American Minimum Requirements and the volumes of material used have always closely approximated, and often surpassed, the volumes required by the new Modified Minimum Requirements of the USA. In fact approximately 20% of all vaccine produced for issue to date has been used in safety tests. All the later batches have subscribed to the latest American requirements.

Nine batches have been completed to date and in none of these batches, either in the monovalent lots or in the final trivalent pools, has live virus been detected either by tissue-culture tests or by monkey inoculations.

There is thus clear evidence provided by adequate tests to prove that the process used is a safe one.

When the Cutter accidents were first reported the Advisory Committee of Experts decided that, besides doubling the strength of formalin solution to be used in

the inactivation process, all safety tests should be repeated before any vaccine was issued. Unfortunately, owing to the addition of chemical preservatives to the finished vaccine, these safety tests could not be repeated on the 7 batches then available. These batches, totalling nearly 200,000 c.c., were thus condemned, not because there was any evidence that they were unsafe, but because the safety tests could not be repeated. This may be regarded as excessive but excusable caution under the circumstances. The remaining 2 batches had no preservative added and so were retested using adequate volumes for tissue-culture purposes. They again successfully passed the tests. These batches have also been tested by the latest potency tests—the S. Gard tests, which are carried out on guinea-pigs —and they have definitely been proved to be antigenic and to provoke the production of significant amounts of protective antibodies. There is, therefore, every sound reason to believe that the vaccine, besides being safe beyond all reasonable doubt, is efficaceous.

It may also be added that in a few children who were inoculated there was a significant antibody response.

CONTROL OF VACCINE IN SOUTH AFRICA

When earlier in the year it became generally known that poliomyelitis vaccine had been apparently successfully manufactured in South Africa, enquiries were made about its release for use.

The Hon. Minister of Health, before deciding on what action was to be taken, sought the advice of a panel of experts. An Advisory Committee of Experts was thus convened. This Committee consisted of the following members: Dr. J. J. du Pré le Roux (Secretary for Health and Chief Health Officer to the Union), Dr. J. H. S. Gear (Director of the Poliomyelitis Research Foundation Laboratory), Prof. M. van den Ende (Professor of Bacteriology, Cape Town), Dr. R. Alexander (Director of Veterinary Services), Prof. J. Barnetson (Professor of Pathology, Pretoria), Prof. H. Snyman (Professor of Medicine, Pretoria), Prof. G. Elliott (Professor of Medicine, Witwatersrand), Prof. J. Brock (Professor of Medicine, Cape Town), Prof. E. Cooper (Professor of Public Health, Cape Town and M.O.H., Cape Town), Dr. H. Nelson (M.O.H., Pretoria), Dr. J. P. de Villiers (M.O.H., Cape Divisional Council), and Prof. R. Turner (Senior Government Pathologist, Cape Town and Adviser in Pathology to the Union Health Department).

This Committee first sat at Cape Town in April 1955, and advised the Minister of Health to await the results of the American Field Trials before making any decisions. As soon as the Francis Report was received the Committee again met and reviewed its contents. It advised the Minister that the report indicated that the vaccine appeared safe and efficacious. In view of the accidents with the vaccine which were just then being reported from the USA, it also advised that the decision as to the issue of any vaccine in South Africa should be delayed.

The Committee again met when a copy of the new American 'Amended Minimum Requirements' was received. It carefully considered these new improved regulations for the safety of the vaccine, and advised that the strength of the formalin in the South African vacine should be doubled, that all safety tests should be repeated according to the new American standards, which it accepted, and that no re-processing of monovalent pools which gave positive culture tests should be allowed. Finally, the Committee met in Pretoria at the end of July. At this meeting it reviewed the report of the Surgeon-General of the Public Health Service of the USA to the Secretary of Health, Education and Welfare, which dealt fully with the investigations into the vaccine accidents which had occurred in the USA and the recommendations that resulted from these investigations. It also studied a copy of a statement issued by the British Ministry of Health on 16 July 1955 following upon the talk given by Dr. G. S. Wilson. This statement said: 'So far it has been found best to abandon the idea of using the original form of the Salk vaccine, but modifications of the Salk-type vaccine are certainly the subject of research. It must be to the abandonment of the original form of the vaccine that Dr. G. S. Wilson was really referring in his reported speech at a luncheon yesterday of the National Fund of Poliomyelitis'.

At this meeting the committee, after careful consideration of all information in regard to the processing and testing of the South African vaccine, and impressed by the fact that active virus particles had not been found by adequate tests in any of the batches so far processed, unanaimously advised the Minister that the South African vaccine had been proved safe beyond all reasonable doubt and was probably efficacious.

On this advice the Minister of Health based his recent radio announcement and his press statement.[13]

A sub-committee was also appointed to consider priorities in the issue of the vaccine on the principles which were laid down by the main committee.

All vaccine manufactured by the Poliomyelitis Research Foundation Laboratories before issue is required to pass stringent tests for purity, potency, and safety as laid down by the Union Health Department, which will regularly inspect the laboratory in reference to all tests. These tests are founded on the latest American Amended Minimum Requirements.

South Africa has thus kept well abreast of all advances in regard to active immunization against poliomyelitis, and appears to have successfully produced a safe and effective vaccine. The money derived from public subscription towards the Poliomyelitis Fund has therefore been well invested and is giving the most promising returns, thanks to the work of Dr. Gear, Dr. Winter, Dr. Malherbe and their small band of assistants. The vaccine is also cheaper to produce in South Africa than it would be to import from the USA if it were available from that country.

The real value of the South African vaccine will be indicated by serological assays carried out on groups of persons who have received the vaccine. It is, however, not practical to carry out field trials in South Africa analogous to those which were carried out in the USA because of the large and expensive organization required and the elaborate laboratory services that are necessary; also because the incidence of paralytic poliomyelitis is so small that a larger population of children than would be readily available in South Africa is required to provide figures for statistical analysis that would, within a relatively short time, be truly significant. Nevertheless, it is the intention of the Poliomyelitis

Foundation Research Laboratory, in cooperation with the Union Health Department, to keep records of all children vaccinated so that in time the value of the vaccine may be accurately assessed.

CONCLUSIONS

The evidence is:

(*a*) That, despite the recent unfortunate accidents with poliomyelitis vaccine in the USA, it is now possible to manufacture consistently a 'killed' formolized vaccine which can be proved by adequate tests, carried out on every batch before issue, to be safe beyond all reasonable doubt.

(*b*) That formolized vaccine has been proved to be of definite value, not in preventing poliomyelitis infections, but in greatly diminishing paralytic complications to this disease. The protection afforded by the vaccine appears to take several months to mature after the primary inoculations. How long the protective hyper-active immune state, which follows upon this immunological experience, lasts is not known but the evidence indicates that it extends over some years. Primary immunization may also be very effectively reinforced by a booster dose of vaccine given 7 or more months after the primary vaccination course of 2 injections.

(*c*) The South African vaccine is adequately tested, has been found safe, and promises to be as effective as the Salk vaccine.

The present formolized killed vaccine is but a most promising commencement of prophylaxis against poliomyelitis. Possibly, in the near future a 'living' attenuated vaccine, to be given by mouth, will be developed that will give better protection, and possibly the role of the formolized 'killed' vaccine will be relegated to providing an initial immunity in infants to be followed up by a more massive immunity induced by a living vaccine given orally. Substantial progress towards the conquest of poliomyelitis has thus been made and the future promises well.

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CHLORAMPHENICOL IN TYPHOID FEVER

A COMPARISON OF THE IN VITRO AND IN VIVO SENSITIVITY OF SALMONELLA TYPHI

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General clinical experience with chloramphenicol in the treatment of typhoid fever has confirmed the report of Woodward *et al.* (1948) that *Salmonella typhi* is susceptible to the drug *in vitro* and *in vivo*. Good and Mackenzie (1950) wrote that selected cultures obtained before, during, and after treatment did not vary in susceptibility to the drug. Even the infecting organism responsible for relapses was not appreciably resistant to chloramphenicol according to Woodward *et al.* (1950).

Sporadic testing at this hospital in previous years had always confirmed the sensitivity of the organism, and routine testing was deemed unnecessary. The recovery of resistant organisms from severely ill patients in January 1954 prompted the comparison of the *in vitro* sensitivity to chloramphenicol with the clinical response to the drug in a series of cases.

MATERIAL AND METHOD

A total of 34 Bantu cases of bacteriologically proven typhoid fever was studied. The main group was a consecutive series of 28 cases personally treated by the author and admitted to Baragwanath Hospital between January and May 1954. There were 13 males and 15 females; their ages ranged from 8 to 40 years, the mean being 21 ·2 years and 7 being children less than 12 years old. Phage-typing of the organisms, performed by Dr. C. G. Crocker, showed that 13 belonged to type A and that 15 were untypable or of miscellaneous types.

Six consecutive cases occurring in November and December 1954 were similarly studied.

The organism was recovered from the patients' blood by bile-broth or clot culture and in some cases from the stool or urine. Sensitivity to chloramphenicol was determined in every case by the dried-disc method; two Dia-Discs (C.S.C. Pharmaceuticals) were used, of a strength of 2μg. and 20 μg. respectively. According to the diameter of the zone of inhibition, reports were issued in the following terms—resistant, moderately sensitive, and highly sensitive—corresponding to minimum inhibitory concentrations of $>9 \cdot 3$ μg., 0·6 to $9 \cdot 3\mu$g., and $<0 \cdot 6$ μg. per ml., respectively.

Limitations of method. The size of the zones of growth inhibition depends on the sensitivity of the organism, the antibiotic content of the disc used, and the rate of diffusion of the antibiotic into the medium. May and Morley (1952) stress that the diffusion of the antibiotic is governed to some extent by the composition and depth of the medium and the amount of surface moisture.

This is a convenient method for routine laboratory work, but in view of the possible fallacies the serial-dilution method was used as a check in some cases. The results were in agreement with those obtained by the disc method.

The method of reporting the results may be misleading because the term resistant is used without quoting the minimal inhibitory concentration and the clinician may be led to assume wrongly that this implies an absolute resistance.

RESULTS

The results of the 28 cases in the first group are shown in Table I. The phage type of the organism does not appear to have influenced the mortality or relapse rates. Twenty-two of the cases fell into the 'resistant' group, in which the mortality rate was 9% (2 deaths) and the relapse rate 18%. The number of cases in the 'sensitive' groups was too small to permit of accurate comparison; there was one death in the 6 cases.

TABLE I

Sensitivity	*Phage Type*		*Clinical Response*		
			Death	*Relapse*	*Good*
Resistant	A	10	1	2	7
	Misc.	12	1	2	9
Moderately sensitive	A	2	—	—	2
	Misc.	3	1	—	2
Highly sensitive	A	1	—	—	1
	Misc.	—	—	—	—

The minimum inhibitory concentrations of $>9 \cdot 3 \mu$g. per ml. in the bulk of the cases exceeded the expected values based on reports on $0 \cdot 25$ μg. by Smith *et al.* (1948), $2 \cdot 5$ μg. by Edge (1950), and $0 \cdot 4$ to $6 \cdot 2$ μg. per ml. by Werner (1954).

An important factor was the clinical grading of the severity of the illness on admission; of 5 cases regarded as very ill, 3 died, 1 recovered after 2 relapses and 1 responded well. Case 2 died of toxaemia 4 days after starting treatment. In case 4 an ulcer perforated after 5 days of treatment, death occurring 3 weeks later. Case 18 was suspected on admission of having perforated and died after 20 days in hospital.

The duration of fever after treatment with chloramphenicol was begun, excluding cases which died or relapsed, averaged $4 \cdot 8$ days, with a range of $2 \cdot 9 \cdot 5$ days.

In case 3 the organism isolated from the stool was at first moderatively sensitive, but cultures made 1 and 2 weeks later were resistant; despite this the patient made a prompt recovery.

In the 6 consecutive cases of the second group, 4 were classed as 'resistant' but nevertheless responded well. One of the 'moderately sensitive' cases responded promptly but the other died; this was a patient who was admitted gravely ill in the 4th week of the disease, and showed no response to chloramphenicol given intravenously. These results confirm the impression that the initial clinical assessment is of more value in prognosis than the *in vitro* sensitivity grading.

DISCUSSION

If *in vitro* sensitivity were a guide to the clinical response it might be expected that the results of treatment would be poor in the 'resistant' group. However, the illness did not follow the course of untreated typhoid fever, and it will be seen from Table II that the outcome compares favourably with other workers' reported series of treated cases. The 19 cases of Hirsowitz's treated group (1951) include the more ill patients. His series comprising young Bantu persons (90% under 30 years of age) drawn from an area served by this (Baragwanath) hospital provides a fair standard for comparison. In view of the wide range of mortality rates quoted for untreated typhoid fever, the duration of fever after the commencement of specific treatment may be a better index for comparison.

The complexity of drug action on susceptible organisms *in vivo* is fully appreciated, involving as it does drug-parasite, host-parasite, and drug-host factors. An ingenious method to overcome some of the limitations of the artificial *in vitro* environment has been used by Werner *et al.* (1954). These authors isolated a bacterial population in the central portion of a triple-layered unenriched 3% agar disc. The discs were inserted into the peritoneal cavities of animal hosts. The bacteria were dependent for growth on nutritive substances from the surrounding tissue fluids and were able to exist in a state more closely approximating to true parasitism than is possible in *vitro*. Even this method does not include properties of the natural lesion such as necrosis, fibrosis and intracellular parasitism; it excludes drug-host factors such as elimina-

TABLE II

Author	*No. of Cases*	*Mortality Rate (as a percentage)*		*Relapse Rate (as a percentage)*		*Duration of Fever (in days)*	
		Treated	*Untreated*	*Treated*	*Untreated*	*Treated*	*Untreated*
Present	22	9		18		4·8	
El Ramli	200	6·3		27·5		3·5	
Hirsowitz	40	15·7	4·7	16·7	28·6	6·5	12·8
Lauckner	32	*nil*	21·3	16·6	4·2		
Osler	1,500		9·1		11·4		
Dubos			15–20		10		

tion or destruction of the drug, binding by plasma proteins, and anatomico-physiological barriers which may impede the passage of the drug from one body compartment to another.

The application of *in vitro* findings to the clinical field is particularly difficult in typhoid fever. Streptomycin for example has inhibited *Salmonella typhi in vitro* in concentrations comparable on a weight basis to those of chloramphenicol, yet the former drug has been notably ineffective in the treatment of typhoid according to Werner *et al.* Another example has been the virtual ineffectiveness of chlortetracycline. Equal serum concentrations of chloramphenicol and chlortetracycline suppressed equally the growth of typhoid bacilli *in vivo*, but the dose of the latter required to produce these concentrations was much higher.

Like the present series, the case reported by Colquhoun and Weetch (1950), despite an initial minimum inhibitory concentration of 12 μg. per ml., did respond although it relapsed. On the other hand Watson (1953), discussing 6 cases treated with chloramphenicol with unsatisfactory clinical response, mentions that all strains isolated were sensitive *in vitro* according to the dried-disc technique.

The conclusion, then, is that the finding *in vitro* of lessened sensitivity to chloramphenicol need not imply a poor clinical response to the drug and should certainly not discourage its use.

I am grateful to Dr. R. Cassel of the South African Institute for Medical Research for permitting the routine sensitivity tests, which were ably performed by Miss G. Shaff and Mrs. van Heerden; and to Mr. R. Boardman for the serial dilution tests.

SUMMARY

Thirty-four cases of bacteriologically proven typhoid fever were studied. Despite the demonstration in *vitro* of lessened sensitivity of the causative organism to chloramphenicol, the clinical response of the patients to the drug was satisfactory.

I thank the physicians at Baragwanath Hospital, especially Dr. L. Hirsowitz, for permission to study cases under their care; also Dr. Mundel of the Johannesburg City Health Department for allowing publication of the results of the phage-typing.

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PREPARATORY EXPERIMENT ON PROTECTION OF SKIN AGAINST IRRADIATION DAMAGE

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Cape Town

For this initial experiment 15 white rats were subjected to different doses of skin irradiation on 3 separate skin areas, and the effect of the oral administration of homogenized spleen (bovine uncooked) was observed over a period of 3 weeks following irradiation. It was found that the rats fed with 100% spleen and 50% spleen remained very lively, and ate very well throughout the experiment. Those on normal diet ate approximately half as much as the spleen eaters, their general appearance seemed to deteriorate, and they were not energetic.

As will be seen from Table I, 6 rats were fed with 100% spleen for 2 weeks before irradiation, and 6 were fed for the same time with 50% spleen and 50% normal rat diet as used in the Animal House of the Department of Physiology, University of Cape Town. Three rats were fed on normal diet before irradiation and continued on normal diet after irradiation. After irradiation the 6 rats on 100% spleen were split into 2 lots: 3 were continued on 100% spleen, and 3 were put on normal diet. The 6 on 50% spleen were split into 2 lots: 3 were continued on 50% spleen and 3 were put on normal diet. It will be noticed that:

(*a*) One of the rats not fed on spleen at all died, and one of the rats not fed on spleen after the irradiation is in a very poor condition.

(*b*) The skins of the rats fed on spleen diet 100% and 50% after irradiation are over-all in better condition than the skins of the rats not fed on spleen after the irradiation. The worst damage is seen in the skins of the rats who had no spleen fed to them before or after irradiation.

This is a preliminary experiment; more details and larger tests are being carried out for confirmation.

TABLE I

Diet	*Rat No.*	*Irradiation Dose (Roentgen)*	*Reaction 21 Days Later*
100% spleen before irradiation and 100% spleen afterwards	1	2,000	E −
		4,000	E −
		6,000	E + −
	2	2,000	E −
		4,000	E −
		6,000	E + −
	3	2,000	E −
		4,000	E −
		6,000	E + −
50% spleen before irradiation and 50% spleen afterwards	1	2,000	E −
		4,000	E −
		6,000	E + −
	2	2,000	E −
		4,000	E −
		6,000	E + −
	3	2,000	E −
		4,000	E + −
		6,000	E + −
Normal diet before irradiation and normal diet afterwards	1	2,000	E −
		4,000	E + −
		6,000	E + + +
	2	2,000	E −
		4,000	E + + +
		6,000	E + + + +
	3	2,000 4,000 6,000	Died after 16 days
100% spleen before irradiation and normal diet afterwards	1	2,000	E −
		4,000	E −
		6,000	E + + +
	2	2,000	E −
		4,000	E + + +
		6,000	E + + +
	3	2,000 4,000 6,000	E − E − E + − Very poor condition
50% spleen before irradiation and normal diet afterwards	1	2,000	E −
		4,000	E −
		6,000	E + −
	2	2,000	E −
		4,000	E + + +
		6,000	E + + +
	3	2,000	E −
		4,000	E + + +
		6,000	E + + +

E − = no epilation. E + − = partial epilation. E + = complete epilation. E + + = complete epilation, slight skin reaction. E + + + = complete epilation, severe skin reaction. E + + + + = complete epilation, severe reaction involving the subcutaneous tissues.

MINISTER OF HEALTH'S STATEMENT ON VACCINATION AGAINST POLIOMYELITIS

The following press statement issued by the Minister of Health the Hon. J. F. T. Naudé was not in the possession of the *Journal* in time for publication before the dates mentioned in it.

As indicated by me in a broadcast speech on 27 July 1955, the poliomyelitis vaccine prepared by the South African Poliomyelitis Research Foundation has been proved to be safe and probably efficacious in combating poliomyelitis and it has therefore been decided to release the vaccine for public use.

It must be clearly understood that vaccination against poliomyelitis will by no means be made compulsory nor is any attempt being made to institute mass immunization this winter. The choice of using the vaccine rests entirely with the individual, or more correctly, with the parents or guardians of children. It has been decided to release the vaccine because there are no unanswerable scientific reasons why this should not be done. We would, therefore, be acting neither as scientists nor as humanitarians if we were to withhold the vaccine from those members of the public who are anxious to use it.

I also indicated in my broadcast speech referred to, that priorities would be determined by a special committee and that issues of the vaccine would for the present be made available for children up to the age of 15 of the most susceptible and/or exposed groups of the population, such as the children of parents whose duties bring them into contact with disease in the course of their work, and all children under the age of 5 years.

Earlier during the year it was announced that sufficient supplies of the vaccine would be available for the country's needs during this winter. However, in view of certain unfortunate occurrences in the United States it was considered advisable, before releasing poliomyelitis vaccine in the Union, to subject it to the latest and most stringent tests for safety and potency. This is a lengthy and exacting process, with the result than an appreciable period of time must of necessity elapse before all the vaccine manufactured can be tested. Consequently the quantity of vaccine which will be available for release this winter is not as great as was originally anticipated and the public will, I feel sure, realize that for the present the vaccine cannot be made available universally.

In the circumstances and on the advice of the special (priorities) committee set up by my Department it has been decided as a first step to determine the country's present requirements in respect of vaccine for children of pre-school age. With this object in view parents of all children not yet attending school who wish their children to be vaccinated against poliomyelitis during this winter by arrangement with their local authority should furnish the latter not later than 17 August 1955 with the name, address and occupation of the parent, and the names and ages of such children. Parents desiring to have their children vaccinated by their own private medical practitioners should also furnish the same particulars to their doctors not later than 17 August 1955. Upon receipt of the above information local authorities should submit to the Director, Poliomyelitis Research Laboratory, Rietfontein, Johannesburg, a schedule showing under the various age-groups up to 5 years the total number of children in respect of whom application for vaccination against poliomyelitis has been made.

These schedules should reach the Director of the Poliomyelitis Research Laboratory not later than 22 August 1955. Private medical practitioners to whom such applications have been made by individual members of the public should also furnish the Director of the Poliomyelitis Research Laboratory, not later than 22 August 1955, with the names, addresses and occupations of the applicants and the ages of the children in respect of whom application for vaccination has been made to them.†

As soon as the aforementioned data have been considered by the priorities committee, local authorities will be advised of the priorities decided upon and the quantity of vaccine which will be allotted to them for immunization purposes.

Private medical practitioners to whom application for vaccination has been made by individual members of the public will likewise be advised of the priorities finally decided upon.

Full directions regarding the method of administration will be issued when the vaccine is supplied.

† The vaccine will as far as possible be made available to private doctors at 1 guinea per 2-dose phial on application to the Laboratory.

EAST LONDON COMPLAINT: FURTHER STATEMENT BY THE MINISTER

The following copy of a letter addressed to the Editor of the "East London Daily Dispatch" has been received by the *Journal* from Dr. L. L. Alexander, Chairman of the East London Division of the Medical Association of South Africa.

SIR,

'The East London Division of the Border Branch of the M.A.S.A., at a recent meeting, unanimously decided to ask you to make the following facts public re the present position of polio, in this country.

'The Institute of Polio. Research—to which the public of the Union of S.A. has donated over £600,000—has produced a vaccine which the Union Health Dept.,—without any trial on humans and without any knowledge at all of long term effects or the length of immunity conferred—has decided to use in mass vaccination. Without any consultation with, or information to, the Medical profession, the Department is almost stampeding the public into having their children vaccinated with a vaccine the effects of which—and this is admitted—may even be harmful and dangerous.

'The gross mishandling of the whole situation and the deliberate withholding of information to the Medical profession, has created a set of circumstances which have thrown grave doubts on the vaccine and has decided the local body of medical men to advise their patients not to submit to vaccination with a vaccine the effects of which are questionable.'

MINISTER'S FURTHER STATEMENT

Following the publication of the above communication the Minister issued the following further statement:

'Under ordinary circumstances, I would not have considered it necessary to reply to the letter of the East London branch of the Medical Association on the subject of the polio vaccine, but unfortunately the letter has been given publicity in the Press and as there may be parents who have applied for vaccine for their children and who may attach importance to the views expressed, I am compelled to give a brief explanation.

'The advice which the doctors of East London may give their patients is, of course, their own responsibility. Against that, however, I wish to make the following statement:

'The public of Southern Africa contributed £600,000 for the establishment of a Poliomyelitis Research Foundation and the Government also makes a contribution towards the maintenance costs and at present subsidizes the production of the vaccine.

'The money was contributed with a view to protecting children against polio by means of a vaccine. The public of South Africa can feel assured that the money which they have contributed has been well spent as the work has been entrusted to persons who are experienced in the study of virus diseases and in the preparation of vaccine, both in South Africa and in the United States, and in respect of whose capabilities in this sphere there are no doubts at all.

EXPERT'S ADVICE

'At the beginning of the year, when strong pressure was exerted on me to release the vaccine to the public, I considered it advisable to appoint a committee of experts in the various branches of medical science to furnish me with the best possible advice because I was deeply conscious of the heavy responsibility which rested on me.

'I also asked our Secretary for Health personally to make a special investigation in the United States with a view to comparing the methods employed there with those in South Africa.

'The advisory committee consisted of Dr. J. J. du Pré le Roux, Secretary for Health, as chairman; Dr. R. Alexander, Director of Veterinary Services, Onderstepoort, and a recognized expert on virus diseases; Prof. J. Barnetsen, professor of Pathology at the University of Pretoria; Prof. J. F. Brock, professor of Medicine at the University of Cape Town; Dr. G. D. Cooper, Medical Officer of Health to the Cape Town City Council; Dr. J. P. de Villiers, Medical Officer of Health for the Cape Divisional Council; Prof. G. A. Elliot, professor of Medicine at the Witwatersrand University; Dr. James Gear, Director of the Poliomyelitis Research Laboratory, Johannesburg; Dr. H. Nelson, Medical Officer of Health, Pretoria; Prof. W. H. Snyman, professor of Medicine at the University of Pretoria; Prof. R. Turner, professor of Forensic Medicine at the University of Cape Town and senior pathologist and adviser on pathological services to the Union Health Department; Prof. M. van den Ende, professor of Pathology at the University of Cape Town and a recognized expert on virus diseases.

'The committee met several times whenever important information in regard to experiments in other countries became available. Their first objective was to determine whether the locally-prepared vaccine was safe. With this object in mind, the method of preparation was examined step by step in order to ensure that a correct and safe method is followed in the present, as well as in future, production of vaccine.

'Thereafter the safety tests, which are repeatedly applied to each batch of vaccine, were investigated to ensure that they comply with the strictest requirements.

'After due consideration of the preparation of the vaccine in South Africa and the particular safety measures observed here and the tests applied here to ensure safety, I, on the unanimous recommendation of the committee of experts, gave the public the assurance that the South African vaccine is considered as safe as any vaccine could be.

'The South African vaccine is prepared by the Polio Foundation exclusively.

'I explained that it would be completely voluntary for parents to make use of the vaccine, and asked that applications should be submitted before August 22 as it is desirable that inoculation should take place before summer.

RIGOROUS TESTS

'The preparation of the South African vaccine differs from the oversea vaccine in that less virulent strains and a higher concentration of the agent which renders it harmless are used. and moreover more rigorous tests are applied. These three factors ensure the utmost possible safety.

'Full information in regard to the degree of efficacy is not yet available in respect of the oversea or the South African vaccine, as this can only be determined after several years of observation.

'In view of the fact that the South African vaccine produced

antibodies in animals as well as in a small number of human volunteers similar to the experience oversea, it can be expected that immunity will be stimulated. As to the duration of this immunity, only time can tell.

'The committee also considered the possibility of the harmful side effects, and in the light of available information of the inoculation of over 6,000,000 children in the United States of America, 900,000 in Canada, and 400,000 in Denmark, has come to the conclusion that the possible dangers are negligible.

REPLY TO EAST LONDON BRANCH

"I now wish to refer briefly to the Press statement of the East London branch of the Medical Association. It is alleged that 'the Union Health Department, without any trial on humans and without any knowledge at all of the longterm effects or the length of the immunity conferred, has decided to use mass vaccination."

'This is untrue. The Department never suggested that inoculation would be complusory and the Department never recommended mass inoculation against the disease. Such a course would in any case not have been possible at this stage as, on account of the particular safety measure and tests which were applied here, there is only sufficient vaccine available to provide for the priority groups as announced by me.

'The Department acted in the public interest by ensuring safe preparation before the vaccine was released; by subsequently making the vaccine available only to those who have applied; by releasing the available vaccine in the first instance to those groups of children who are the most exposed to the disease; and by subsidizing the production of the vaccine so that it will be available even to the poorest sections of the population.

'It is interesting to find that in the short period (as already indicated, the closing date had to be early) 427 medical practitioners have applied for the vaccine for nearly 13,000 private patients and of this number 156 doctors have applied to have their own children inoculated.

'I have personally visited the Polio Research Institute and have seen how the vaccine is prepared and tested and on the advice of the committee of experts I was completely reassured and have applied to have my son inoculated.

OWN CHILDREN INOCULATED

'Moreover, every member of the committee who has responsibilities towards children in their own families have decided to have their children inoculated. It is significant that 12 children of members of the staff of the Institute were inoculated some time ago without any ill effects.

'This is also an answer to the allegation by the East London doctors that the vaccine has not been tested on humans.

'In conclusion I wish to state that neither I nor the Department, and I understand the Polio Research Institute—was approached by the East London branch or any of its members for any information, and I don't follow their allegation that "without any consultation with, or information to, the medical profession the Department is almost stampeding the public into having their children vaccinated'."

'It is obviously not possible to consult each individual doctor—many of them have limited knowledge of the subject—and the best course was therefore considered to call on the advice of a number of properly qualified experts.

'There is something in the statement of the East London Branch which I cannot regard as anything but malicious, and that is the allegation that the Department "is almost stampeding the public into having their children vaccinated with a vaccine, the effects of which—and this is admitted—may even be harmful and dangerous."

'Who admitted this—or who suggested it? It is a totally incorrect and misleading statement and a more irresponsible assertion is difficult to imagine.

'I therefore leave it to the thinking public of South Africa to decide whether the Department of Health was justified to act on the advice of a committee of experts in this particular sphere, and to recommend that it is not unsafe to use the vaccine prepared by an institution to which the public themselves contributed funds for this purpose, or whether the advice of a small number of doctors, who admit that they are not informed and who consequently cannot judge, should be preferred and followed." — S. A. Press Association.

CONGRESS NEWSLETTER : KONGRESNUUSBRIEF

With Congress only 2 months away now, we are pleased to announce that the response to the Intermediate Circular was most heartening—so much so that it has become necessary to close the lists of the Congress Banquet, and members wishing to make late reservations for this function will have to be content with provisional bookings, subject to cancellations. The Game Reserve trip too, has proved most popular and only a limited number of vacancies now exist.

Congress week will be taken up with a round of social functions, not the least of which will be the arrangement of alumni dinners and luncheons. The Manchester and Liverpool alumni luncheon will be held at the Pretoria Country Club on Tuesday, 18 October, and arrangements are being made for Guy's, Barts and Oud Studente Nederland *inter alia* to dine together that evening. All members interested in these luncheons and dinners must please communicate with the Organizing Secretaries as soon as possible to facilitate arrangements.

The response to the scientific papers has been excellent and meetings have been arranged for all the 19 sections. On this occasion there have been a large number of papers provided by the general practitioners' section and, generally, the number of papers is considerably more than can be accommodated and it is with regret that the Organizing Committee has had to reject some of the papers offered.

The Cerebral Palsy movement in South Africa has now received recognition by the Government and the 3 schools in operation are being recognized by the Department of Education, Arts and Science as State-aided schools. The Organizing Committee of Congress has taken this opportunity of placing the problem of cerebral palsy before the medical profession in South Africa and arrangements have been made for a symposium on the subject. One of the world's leading authorities on cerebral palsy—Mr.

Die Kongres vind oor 2 maande plaas, en ons is bly om aan te kondig dat lede goed gereageer het op ons Tweede Omsendbrief—so goed dat die lyste van die Kongresbanket afgesluit moes word. Lede wat laat besprekings vir hierdie funksie wil maak sal met voorlopige reservasies, onderworpe aan kansellasies, tevrede moet wees. Die Wildtuin-toertjie het baie populêr geblyk, en slegs 'n beperkte aantal kan nog opgeneem word.

Die Kongresweek is sosiaal vol bespreek, en die Alumni-dinees en noenmale tel onder die belangrikste afsprake. Die Manchester en Liverpool Alumni-noenmaal word op Dinsdag 18 Oktober by die *Pretoria Country Club* gehou, en reëlings word getref vir 'n gesamentlike dinee op daardie datum vir Alumni van die Guy-hospitaal, Barts en die Oud-Studente Nederland. Alle lede wat in hierdie dinees en noenmale belangstel, moet gerieflikheidshalwe so gou moontlik met die Organiserende Sekretarisse in verbinding tree.

Reaksie i.v.m. wetenskaplike verhandelinge was uitstekend, en 'n vergadering is gereël vir elk van die 19 afdelings. By hierdie geleentheid is 'n groot aantal verhandelinge van algemene praktisyne ontvang, en oor die algemeen is soveel verhandelinge ontvang dat die Organiserende Komitee tot hul spyt party daarvan van die hand moes wys.

Die Spastiese Verlamming-beweging in Suid-Afrika het nou erkenning van die Regering ontvang, en die 3 skole tans in werking word as staatsondersteunde inrigtings erken deur die Departement van Opvoedkunde, Kuns en Wetenskap. Die Organiserende Komitee van die Kongres maak van hierdie geleentheid gebruik om die vraagstuk van spastiese verlamming aan die mediese beroep in Suid-Afrika voor te lê, en reëlings vir 'n samespreking oor hierdie onderwerp is getref. Een van die wêreld se vooraanstaande gesaghebbendes op hierdie gebied, mnr. G. A. Pollock van Edinburgh, het goedgunstiglik ingestem om aan die samespreking

G. A. Pollock of Edinburgh—where the Westerlea School for Cerebral Palsy is recognized as one of the leading institutions of its kind in the United Kingdom—has kindly consented to take part in the symposium.

It is with much pleasure that the Organizing Committee announces that Dr. M. G. Candau, the Director General of the World Health Organization, will visit South Africa during October, and that he will address Congress at 4.30 p.m. on Monday, 17 October. He will be accompanied by the Director of the World Health Organization in Africa (Dr. F. Cambournac) from Brazzaville.

Dr. Candau was born in Rio de Janeiro, Brazil, in 1911. He obtained his medical degree at Rio de Janeiro, and received special training in public health at the University of Brazil and at Johns Hopkins University, Baltimore, U.S.A.

Dr. Candau served in the Brazilian public health service and from 1934 to 1943 was in charge of various health services in the State of Rio de Janeiro, ultimately becoming Assistant Director of that State's Department of Health. Between 1943 and 1950 he was Director of Division, Assistant Superintendent, and later Superintendent, of the Servico Especial de Saude Publica, a cooperative health service established by the Brazilian Government together with the Institute of Inter-American Affairs. In 1938 he was appointed Assistant Professor of Hygiene at the School of Medicine, State of Rio de Janeiro, and, in 1948, Assistant Professor of Epidemiology in the National Health Department.

Dr. Candau joined the staff of the World Health Organization at Geneva in 1950 as Director of the Division of Organization of Health Services. Within a year, he was appointed Assistant Director-General in charge of Advisory Services. In 1952 he moved to Washington as Assistant Director of the Pan-American Sanitary Bureau, which is also the Regional Office of the World Health Organization for the Americas. While occupying that position, he was elected by the World Health Assembly to become the second Director-General of the World Health Organization. He took up his post in Geneva in July 1953.

Dr. Candau is the author of several scientific papers covering a wide range of subjects, among them malaria, parasitology, public health administration, bio-statistics, rural hygiene, etc. He is an Honorary Fellow of the American Public Health Association, the Royal Sanitary Institute, Great Britain, the National Academy of Medicine, Peru, the Peruvian Public Health Association, and the Royal Academy of Medicine, Ireland; and a Member of the Brazilian Society of Hygiene, the Society of Medicine and Surgery, State of Rio de Janeiro, the Royal Society of Tropical Medicine and Hygiene, Great Britain, and the Inter-American Association of Sanitary Engineering.

deel te neem. Die *Westerlea School for Cerebral Palsy* te Edinburgh staan bekend as een van die belangrikes van sy aard in die Britse Ryk.

Die Organiserende Komitee kondig met genoeë aan dat dr. M. G. Candau, Direkteur-Generaal van die *World Health Organization*, gedurende Oktober besoek aflê aan Suid-Afrika, en dat hy om 4.30 nm. op Maandag, 17 Oktober die Kongres sal toespreek. Hy word deur dr. F. Cambournac van Brazzaville, Direkteur in Suid-Afrika van die *World Health Organization*, vergesel.

Dr. Candau is in 1911 in Rio de Janeiro, Brasilië, gebore. Daar het hy sy mediese graad behaal, en hy het verder spesiale opleiding in volksgesondheid aan die Universiteit Brasilië en die Johns Hopkins-universiteit, Baltimore, V.S.A. ontvang.

Dr. Candau het in die volksgesondheidsdienste van Brasilië gewerk, en vanaf 1934 tot 1943 was hy verantwoordelik vir 'n aantal gesondheidsdienste in die Staat Rio de Janeiro. Later het hy Assistent Direkteur van daardie staat se departement van volksgesondheid geword. Tussen die jare 1943 en 1950 was hy Divisie-Direkteur, Assistent Superintendent en later Superintendent van die *Servico Especial de Saude Publica*, 'n koöperatiewe gesondheidsdiens wat deur die regering van Brasilië en die *Institute of Inter-American Affairs* in die lewe geroep is. In 1938 is hy aangestel as Assistent Professor van Higiëne by die mediese skool van die Staat Rio de Janeiro, en in 1948 Assistent Professor van Epidemiologie in die Nasionale Departement van Volksgesondheid.

In 1950 het dr. Candau as Direkteur van *Division of Organization of Health Services* by die personeel van die *World Health Organization* aangesluit. Binne 'n jaar is hy aangestel as Assistent Direkteur-Generaal verantwoordelik vir die *Advisory Services*. In 1952 is hy na Washington as Assistent Direkteur van die *Pan-American Sanitary Bureau*, wat ook as die Streekhoofkantoor van die *World Health Organization* vir die Amerika's dien. Terwyl hy hierdie amp beklee het, het die *World Health Assembly* hom verkies tot tweede Direkteur-Generaal van die *World Health Organization*. Hierdie amp het hy in Julie 1953 in Genève aanvaar.

Dr. Candau is die skrywer van 'n hele paar wetenskaplike verhandelinge oor verskeie onderwerpe, waaronder malaria, parasiteleer, volksgesondheidsadministrasie, biostatistieke, plattelandse higiëne, ens. Hy is 'n ere-Fellow van die *American Public Health Association*, die *Royal Sanitary Institute* van Groot Brittanje, die *National Academy of Medicine* in Peru, die *Peruvian Public Health Association* en die *Royal Academy of Medicine* van Ierland. Hy is ook lid van die *Brazilian Society of Hygiene*, die *Society of Medicine and Surgery* van die Staat Rio de Janeiro, die *Royal Society of Tropical Medicine and Hygiene* in Groot Brittanje, en die *Inter-American Association of Sanitary Engineering*.

PASSING EVENTS : IN DIE VERBYGAAN

Research Forum, Groote Schuur Hospital. On 7 September the Speaker will be Mr. T. Schrire and the subject of his paper will be 'The Effect of the Sun's rays on the face and lips'.

* * *

Dr. H. P. J. (Hennie) Pretorius, M.B., Ch.B., van die Departement Kindergeeskunde, Algemene Hospitaal, Pretoria, het 'n aanstelling ontvang vir 'n jaar in dr. Lee Emmett Holt, jnr. se Kinderkliniek in die Bellevue-hospitaal, New York, V.S.A. Hierdie aanstelling is moontlik gemaak deur 'n beurs van die Wetenskaplike en Navorsingsraad.

Dr. Pretorius beoog ook om ander kinderklinieke, o.a. te Baltimore, te besoek en om daarna na Europa te gaan vir 'n verdere 6 maande om sy studies af te rond.

* * *

Mr. S. Shulman, F.R.C.S. (Edin.), and Miss C. Wadham were married in Cambridge, England, on 23 July 1955.

PETHIDINE ADDICTION : WARNING BY WHO EXPERT COMMITTEE

Dr. M. G. Candau, Director General of the World Health Organization, has requested through the World Medical Association that the medical profession of the world be informed of the findings of its Expert Committee relative to pethidine addiction. In part, the report dated 9 May 1955, which was adopted by the Executive Board of the World Health Organization at its 5th Session, reads as follows:

'The Expert Committee on Drugs Liable to Produce Addiction, having considered a report on pethidine addiction as encountered at the Public Health Service Hospital, Lexington, Kentucky, U.S.A., and noting the high incidence of such addiction among members of the medical, nursing and associated professions, considered that an important factor in the development of pethidine addiction not only in the United States of America but also in other countries has been the attitude of physicians towards the drug, based upon the widespread belief that it is less dangerous in this respect than morphine.

'Being convinced that experience with the drug, both in experi-

ments and in clinical practice, is contrary to this belief, the Expert Committee was of the opinion that pethidine is as dangerous as morphine as a potential addicting agent, that its use should be undertaken only with full realization of this danger, and that its administration should be approached with the same attitude and attended by the same precautions as are recognized for morphine, and therefore urged that the Director General, by whatever means he might deem appropriate, bring to the attention of governments and the medical profession throughout the world the dangerousness of the addiction potentiality of pethidine, and the need for the same care in its use as with morphine'.

Further information on the subject will be found on pages 13-16 of WHO Technical Report Series No. 95 (*Expert Committee on Drugs Liable to Produce Addiction*). A commentary was published in this *Journal* on 2 July 1955 (S. Afr. Med. J., **29**, 629).

IN MEMORIAM

LIONEL BERNARD GOLDSCHIMDT, B.A., LL.D. *hon. causa* (RHODES UNIV.), M.B., B.S. (LOND.), F.R.C.S. (ENG.)

As announced in the *Journal* of last week, the death of Mr. Goldschmidt took place at his Cape Town residence on 19 August.

Lionel Bernard Goldschmidt

Mr. Goldschimdt was born in Queenstown, E.P., 63 years ago. He took his arts degree at Rhodes University College, Grahamstown, and proceeded to London, where he studied medicine at King's College Hospital. His career as a medical student was interrupted in 1914 by World War I, when Goldschmidt enlisted in the London Rifle Brigade and went to France with the first 100,000 (he was a corporal) and fought at Mons. He later returned to his medical school and qualified M.R.C.S., L.R.C.P. in 1917, when he went into the Indian Medical Service. In the Gallipoli campaign he served as medical officer on a troopship.

In 1918 he graduated M.B., B.S. (Lond.) and after serving house appointments at King's College Hospital he held the position of Sambrooke Surgical Registrar with distinction; at this time he worked under Sir John Thompson-Walker and Mr. John Everidge.

Also in 1918 he married Miss Nora Rosalie Adlington, of Worcester, England. He proceeded F.R.C.S. in 1921. On the death of his father he decided, in spite of opportunities to pursue a surgical career in London, to practise urology in Cape Town, where he settled in 1922. He was appointed honorary surgeon at the Somerset Hospital in 1930 and for many years was head of the Department of Urology at the University of Cape Town and Groote Schuur Hospital, from which position he retired in 1947.

In the Medical Association of South Africa Mr. Goldschmidt commanded high respect and wielded great influence. For many years he was a member of the Federal Council and the Cape Western Branch Council, and was President of the Branch in 1945. He took a leading part in the foundation of the College of Physicians and Surgeons of South Africa and was chairman of the special committee of the Association dealing with that matter until he was compelled to resign by ill-health.

Mr. Goldschmidt commanded the respect of his medical colleagues, his patients and the public in the very highest degree. His interests however were by no means confined to medical matters. He was actively associated with the South African Red Cross Society for many years, was Regional Commissioner at one time, and took a leading part in the institution of the Red Cross War Memorial Children's Hospital at Rondebosch, Cape. In World War II. he was honorary colonel in the 3rd Field Ambulance. He was vice-president of the Boy Scout Association.

Mr. Goldschmidt was a great hunter and photographer of wild animals and travelled widely in Africa in pursuance of this interest. For some years he was president of the Cape Town Philatelic Society and was at one time on the Boxing Board of Control. He was interested in farming and played golf and formerly tennis.

His is survived by his wife, two daughters (Mrs. Pieter Melck and Miss Elizabeth Goldschimdt) and two sons (Dr. Basil Goldschmidt and Mr. Reith Goldschmidt, a medical student at King's College Hospital, London.

Dr. R. Lance Impey of Cape Town, writes: With the passing of Lionel Goldschmidt the medical profession in South Africa has lost a great leader. Service was the dominant note of his life.

Not satisfied with his personal success as a surgeon, he devoted a great part of his time and energies to the interests of his profession, and in endeavouring to advance the art of surgery.

It is due to Goldschmidt and a number of other South African surgeons—Barnard Fuller, Ken Frater, Peter Moll and Peter Roux, to name a few—that surgery in this country occupies its present proud position.

It had long been recognized that no individual surgeon can possibly master all of the various branches of surgery. Attempts to keep South Africa in line with modern developments in this respect met with formidable opposition, but Goldschmidt and his colleagues persisted in a crusade which has resulted in the full development of the surgical specialities in this country.

Goldschmidt's success as a surgeon was not only due to his skill, but to his remarkable personality. In a long life of medical practice one has seldom met a doctor who has inspired his patients to the extent that he did.

At the outbreak of World War I, while still a medical student, Goldschmidt joined up as a combatant and fought at Mons. After qualifying in medicine he joined the Indian Medical Corps and served to the end of the war. Though not in the army during the last war, he was employed in a part-time capacity by the S.A.M.C. as a genito-urinary specialist and gave his expert services throughout the war, but refused to accept any remuneration.

For the past 30 years he served continuously on one or other of the committees of the Cape Western Branch of the Medical Association of South Africa, and also on the Federal Council.

Although he is no longer with us he will ever remain in our memories, having left an example of service that will continue to inspire us.

Mr. J. A. Currie of Cape Town, writes: The passing of L. B. Goldschmidt at the relatively early age of 63 removes a striking and distinguished figure from the urological scene in South Africa. Responsible as he was for a unique feeling of group fellowship amongst urologists, particularly in the Cape, he started a Tuesday discussion session in his department at Groote Schuur, which is continued to this day and is attended by all the urologists in Cape Town. Here a spirit of emulation and friendliness relieves the stresses of private practice and a bond is created between all urologists.

To Goldschmidt a urologist was necessarily a friend. To have been his house surgeon was to be certain of his support and encouragement in the future and his generous outlook and absence of pettiness gave confidence to many an embryo urologist. He helped his younger colleagues on their way with unfailing kindness and frequently to the detriment of his own interests.

Those who worked with him soon learned to recognize the careful logic of his diagnostic reasoning, his dexterity with instruments and his skill in interpreting radiological and cystoscopic appearances. But he was no mere endoscopist. His general clinical

judgment and great skill in operating would have made him a first-class general surgeon.

Goldschmidt possessed the enviable gift of inspiring his patients with unbounded confidence in everything he said or did. This gift and his great skill and knowledge built up for him a formidable reputation, which remained with him throughout his years of practice.

His interests apart from his profession were so numerous that one wonders at his ability to maintain them all. As a hunter, a fisherman, a golfer or a farmer, a photographer or a philatelist he was equally enthusiastic. His tall, slightly stooping figure could bend nearly double over a cystoscope, or straighten out and become remarkably efficient at some game or sport.

His numerous activities on committees revealed a clear grasp of affairs. Never garrulous, he had the gift of knowing the psychological moment for speech and his interventions were telling, usually forcible, and confident.

He enjoyed to the full an active social life and was hospitality itself in his own home.

In this life of service, achievement and active enjoyment he was sustained throughout by the happiest of family lives. To his children and to his devoted wife our deepest sympathy goes out in this time of loss.

Mr. S. Scher, of Cape Town, writes: It was with deep regret and sorrow that I heard of the passing of Mr. L. B. Goldschmidt. His death has removed an outstanding personality from the medical profession, not only of Cape Town but of the whole of Southern Africa.

I first met Mr. Goldschmidt on my return to Cape Town in 1934 and had the pleasure and privilege of working under him for many years. Our association during all these years was a most pleasant one. As a surgeon and operator he was brilliant and outstanding. This was well recognized by the profession and the public, giving him one of the most successful and busy practices in Cape Town. He organized the Department of Urology at Groote Schuur Hospital and must be regarded as the true founder of the speciality of Urology in Cape Town not only on account of his worth and example, but also because of the help and encouragement he gave to most of the urologists at present practising in the Mother City. In spite of his heavy professional responsibilities he still found time for many extraneous activities, which exemplified his deep interest in the country of his birth.

He had a generous and kindly nature and was of a cheerful and happy disposition, but his heavy responsibilities ultimately took their toll and he sacrificed himself on the altar of service to his fellow man. I had the privilege of visiting his home on many occasions when it was obvious his home life was a very happy one. He was blessed with a brave and devoted wife who was a great help to him. Our sincere condolences are offered to her and her family in their sad and heavy bereavement.

ASSOCIATION NEWS : VERENIGINGSNUUS

Full-time Hospitals and Universities Medical Officers Group
A Cape Western Sub-group of the Full-Time Hospitals and Universities Medical Officers Group of the Association has been formed. The present office-bearers are: *Chairman*—Dr. S. Berman, *Vice-Chairman*—Dr. C. Merskey, *Hon. Secretary-Treasurer*—Dr. C. S. Jones, *Committee members*—Prof. R. H. Goetz, Dr. M. Grieve, Dr. W. P. H. Jackson and Dr. P. M. Smythe.

The annual subscription (covering subscriptions to the parent body and the Sub-Group) is 5s. and any members of the Medical Association who are full-time officers in the service of the Universities or the Provincial, Government or Municipal Hospitals and who wish to join the organization may apply to the Secretary at the Department of Anaesthesia, Groot Schuur Hospital, Observatory, Cape for information and for enrolment.

CORRESPONDENCE : BRIEWERUBRIEK

REPUDIATION OF FEES BY MEDICAL AID SOCIETY

To the Editor: With the ever-increasing number of medical aid societies, the matter of cooperation between their administrative staff and the medical practitioners is a very important one to those engaged in private practice. While in the majority of cases the scheme is working satisfactorily, there are certain medical aid societies whose secretaries appear, to say the least of it, to be entirely uncooperative and to be breaking the spirit, if not the letter, of the original agreement between the medical profession and the medical aid societies. This has not only been my personal experience but that of a large number of my colleagues, who are constantly complaining about the small technical points on which some medical aid societies are refusing to pay accounts, leaving the onus on the practitioner to collect the account, for which a reduced fee has been charged and which often is irrecoverable. While it is fully appreciated that regulations and rules must be kept, the endless delays and procrastinations on the part of a small minority of these medical aid societies are causing endless inconvenience and frustration as well as financial loss. I would like, while all the details are fresh in my mind, to cite one particular case which appears, after discussion with colleagues, to be typical of many.

A patient was referred by his general practitioner 11 months ago as a medical aid society case. He was seen, and a report was forwarded to the doctor concerned in the usual way. For the first 3 months accounts were sent to the patient. On the 4th month an account was sent to the local secretary of the medical aid society with 'kindly investigate' written across it, in accordance with instructions in the Medical Aid Society Handbook. The 5th month's account was sent to the Durban secretary of this medical aid society in a similar manner. The 6th month's account was sent to the secretary of the medical aid society's headquarters in Johannesburg also with 'kindly investigate'. No reply was received to any of these communications. My secretary twice telephoned the local secretary of the medical aid society, who said the matter was not their concern but they would convey the message to the relevant department. Two months later I myself spoke to them. Still no satisfaction was received. Eventually, 10½ months after seeing the patient, a curt note was received from the medical aid society secretary concerned—the first acknowledgment received from this secretary—stating that, as the patient had broken the rules of the medical aid society, the society would not hold itself responsible for the fee and I was advised to collect the fee from the patient. A strong letter of protest was written by return to the secretary giving all the details of the case and pointing out that this was a flagrant breach of the agreement between the profession and the societies. This letter was written over 2 weeks ago and no reply has as yet been received.

How long is the medical profession to put up with this treatment? We give our services at a reduced rate and in return every legal loophole in cases such as this is used to evade paying the fee due. In this particular case a business friend assessed the expenses involved so far in trying to recover a £2 2s. 0d. fee as follows: Stamps 1s. 10d., telephone calls 1s. 0d., stationery 6d., Interest on overdue account 2s., secretary and bookkeeper's time wasted 3s. 6d.; total 8s. 10d. This does not include wear and tear on the doctor or the very natural feeling of annoyance and frustration at what is, to the doctor's way of thinking, petty fraud.

We are not trained business men and cannot hope to compete with shrewd business men in their own subject. They will always be able to find loopholes if they wish or to delay payment until, in desperation, the doctor writes the account off as a bad debt to save himself and his bookkeeper further trouble.

I feel that the Association should consider employing a full-time solicitor to safeguard our interests in such matters. If this attitude on the part of certain medical aid societies persists, the Association must take a firm line immediately to protect the interests of its members. It would be interesting to know whether other colleagues in different parts of the country are experiencing similar difficulties.

Fair Play

17 August 1955